CHARACTERISTICS AND OPTIMAL COMBINATION PHARMACOTHERAPY FOR NEWLY-TREATED PATIENTS WITH DIABETIC PAINFUL NEUROPATHY

by

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ABSTRACT

To compare patient characteristics and healthcare costs between newly-treated DPN patients receiving mono-pharmacotherapy and those receiving combination pharmacotherapy.

A patient cohort was identified diagnosed with DPN during 2006-2013 in Inovalon's MORE2® registry, a healthcare data warehouse with national medical/pharmacy claims, continuously enrolled for at least 18 months. Patients were included if they were ≥18 years at the time of their first DPN prescription for a tricyclic antidepressant (TCA), opioid, duloxetine, gabapentin, pregabalin, or any route lidocaine. They were classified as having mono- or combination pharmacotherapy (time between the first and second medicine was within 30 days). If there was a 60-day prescription fill gap, the prescription was classified as discontinued. Switch or add-on groups were categorized based on continuation of the index medicine. A simple proportional hazards model was conducted for comparing time to discontinue, switch, or add on. Multiple logistic regression was used for identifying predictors of combination pharmacotherapy.

There were 7,145 patients on mono-pharmacotherapy and 421 patients on combination pharmacotherapy. The top three index medicines were gabapentin (55.7%), opioids (13.1%), and pregabalin (12.9%) in the mono-pharmacotherapy group, and opioids+gabapentin (27.1%), TCAs+gabapentin (17.6%), and duloxetine+gabapentin (8.6%) in the combination group. Patients on combination pharmacotherapy were 130%

more likely to discontinue their medications than patients on mono-pharmacotherapy. There was no statistically significant difference in time to switch (p=0.254) and add on (p=0.069) between mono- and combination pharmacotherapy. Patients who were female, with >7 co-morbidities, and who had depression or arthritis were more likely to start with combination pharmacotherapy. Patients who were older than 65 and those with hypertension were less likely to start with combination pharmacotherapy. The total post-minus pre-index cost had no statistically significant difference between mono- and combination pharmacotherapy (p=0.66).

Newly-treated DPN patients should add on another medication sooner than 30 days when considering combination pharmacotherapy. Because all first-line medications have similar efficacy, the cost should be considered in the treatment decision. For this reason, gabapentin and TCAs are recommended. If considering the pre-index costs, taking combination pharmacotherapy will not cost more money; the policy maker can reimburse either gabapentin+opioid or TCA+gabapentin.

To my grandmother

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CHAPTER 1

BACKGROUND

1.1 Epidemiology and Burden of Diabetic Painful Neuropathy

1.1.1 Definitions of DPN

The United States is experiencing a diabetes epidemic. In 2012 approximately 29.1 million Americans, or 9.3% of the population, had diabetes mellitus (DM) - a disorder of carbohydrate metabolism.[1] Approximately 60 to 70% of DM patients develop peripheral neuropathy. Peripheral neuropathy is the most common complication of DM, followed by retinopathy and nephropathy.[2] Diabetic neuropathy patients can be grouped into focal and diffuse groups. The diffuse group includes patients with chronic and progressive pain, and is more common than focal neuropathies.[3] Diffuse neuropathy patients can have either distal symmetrical sensorimotor polyneuropathy (DSPN) or diabetic autonomic neuropathy.

Some DSPN patients lose some or all sensation without pain, feeling tingling or numbness.[4] About half of the patients who lose sensation in affected areas will develop diabetic painful neuropathy (DPN) as well.[4] For those who experience pain, there are different categories of neuropathic pain depending on the symptoms and signs. The first is spontaneous pain, which presents in the absence of any stimulation; it is usually described as shooting, stabbing, or electric shock-like in quality. The second is stimulus

evoked pain, which presents in response to either a normally nonpainful stimulus (allodynia), or as having an increased pain response to a normally painful stimulus (hyperalgesia). The third and fourth are abnormal sensations in neuropathic-pain patients, paresthesia and dysesthesia, which are described as itching, numbness, tingling, and pins-and-needles sensations.[5] A cross-sectional cohort survey (painDETECT) conducted in Germany presented the following clinically relevant symptoms of DPN: prickling (35%), burning (33%), numbness (30%), pain (29%), pressure (22%), and allodynia (18%).[6] Due to the variety of clinical symptoms, clinicians define DPN in different ways, resulting in DPN not having universally accepted criteria for diagnosis. Therefore, there is no standard rate of prevalence among diabetic patients in clinical practice.[7] One 2011 community-based study (n=15,962) assessed DPN through neuropathy symptom scores (NSS) and neuropathy disability scores (NDS) and reported the prevalence of the disease as 21% in the UK.[8] Another UK multicenter study (n=6487) assessed DPN through NSS and NDS and reported the prevalence of DPN as 28.5% in diabetic patients.[9] Overall, the prevalence of DPN is around 20-30% in diabetes patients.

The pathogenesis of DPN remains unknown. Potential mechanisms include the following: increased blood glucose instability,[10] increased peripheral nerve epineurial blood flow,[11] altered foot skin microcirculation,[12] reduced intraepidermal nerve fiber density,[13] increased thalamic vascularty,[14] and autonomic dysfunction.[15] There are multiple mechanisms involved in the pathogenesis of DPN, which seem to be mutually interconnected and act in a synergistic way. That is to say, DPN is not the result of a single etiology or a specific lesion, but is produced by heterogeneous conditions.

The clinical correlates of DPN are age, body mass index, waist circumference, physical

activity, diabetic nephropathy, dyslipidemia, peripheral arterial disease, and the severity of sensorimotor deficits.[3] The National Diabetic Information Clearinghouse also stated patients who have had DM for 25 years or longer have the highest rates of neuropathy.[16]

1.1.2 Co-morbidities of DPN

Cardiomyopathy, nephropathy, and retinopathy are the most common co-morbidities of DM in DPN patients. Foot ulcers and infections also occur and may lead to nontraumatic lower limb amputations.[5] A study from Kaiser Permanente Colorado assessed DPN co-morbidities between 1998 and 2003; Ritzwoller found that there was an almost ten-fold higher rate of limb amputations and more than twice the incidence of limb infection for pain-experiencing DPN patients compared to nonpainful DM patients.[17] Mental disorders are also a common co-morbidity of diabetes mellitus in DPN patients. A systematic review conducted by Egede et al. concluded that individuals with Type 2 DM (T2DM) were 60% more likely to be diagnosed with depression than those without T2DM.[18] Multiple co-morbidities are the common clinical characteristics in DPN patients. Sadosky et al. described the average number of co-morbidities as 3.1± 2.18 in DPN patients.[19] A 6-month, multicenter study conducted in Germany found that 89.5% of DPN patients reported co-morbidities, including hypertension (70.5%), hyperlipidemia (39.2%), depression (24.8%), retinopathy (9.2%), and nephropathy (9.1%) .[20] Similar data were seen in one US study which reported higher rates of hyperlipidemia (70%) and rheumatism (60- 64%).[21]

1.1.3 Quality of Life of DPN

DPN affects patients' health-related quality of life (HRQoL) and functioning causing clinically important disability, distress, anxiety, and sleep disorders.[22] In a UK HRQoL study, the neuropathic pain was confirmed through a Self-complete Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) questionnaire. The bodily pain of the cohort was assessed through a Medical Outcomes Study 36-item short form (SF-36),[23] and the scores of neuropathic pain (40.99) were statistically lower than for chronic pain (55.77) and no chronic pain (84.78) ($p<0.001$). Even after adjusting for age and pain severity, the HRQoL in neuropathic pain patients (48.89) was still poorer than in chronic pain patients (54.44), on a scale of zero to one hundred with zero meaning no pain and one hundred meaning pain as bad as the patient could imagine.[24] The same study showed neuropathic pain was associated with every dimension of general health: physical functioning, physical role, bodily pain, general heath, vitality, social functioning, emotional role, and mental health. Overall, the HRQoL in DPN patients is poor, and the pain affects most aspects of their daily life.

1.1.4 Costs of DPN

The burden of DPN is expected to rise as diabetes becomes more prevalent in an aging and overweight population. A recent observational UK study reported that the annual incidence of DPN increased over 2006 to 2010 from 2.7 to 3.8 per 100,000.[25] While this differential incidence in DPN may appear unimportant, the cost of the disease is life-long. Total medical costs assessed for DPN at Kaiser Permanente Colorado were $14,062 per patient per year in 2003, higher than nonpainful diabetic neuropathy patients

($6,651), because patients with DPN encountered a higher proportion of hospital costs relative to any other category of utilization costs. Total annual costs were increased with female gender, older age, and co-morbidities.[17] One 2006 IMS Health & Medstat study in the US reported that the average annual costs of patients with DPN were significantly higher than those with the matched underlying disease (Medstat: $40,705 vs. $30,349; IMS Health: $22,754 vs. $16,467).[26] Dworkin et al. reported that the much higher health-care costs in the Medstat group compared to the IMS health group were due to the patients in the Medstat group being generally older and having more co-morbidities. The average annual 2007 pain medication cost for DPN patients was reported as $1,004 in one retrospective study.[27]

In addition to the high costs of DPN care, these patients also have high levels of healthcare resource utilization including physician visits, hospital stays, and medicine use.[22] Gore et al. showed that one-third of DPN patients had a hospitalization, and 39% of them utilized ER services.[21] Furthermore, Ritzwoller found that pain-experiencing DPN patients had 2.5-fold higher hospital admission rates than nonpainful DPN patients.[17]

Nevertheless, DPN also leads to higher indirect costs resulting from work loss — mainly absenteeism, presenteeism, or reduced productivity in the workplace.[28] Stewart et al. reported that symptomatic DPN patients lost 1.4 more hours of work per week than the patients without symptomatic DPN ($p<0.05$).[28] Tolle et al. found approximately one-third of the DPN patients (35%) had lower employment status: reduced work time (15%), disability (12%), unemployment or early retirement (8%).[29] Overall, the annual indirect DPN costs were $3.65 billion measured by the Caremark Work and Health Interview

(WHI) during August 2001 to February 2004, which was calculated by multiplying lost hours by self-reported hourly earnings.[28] The WHI is a validated computer –assisted telephone interview that measures lost productive time and its health-related causes.[30]

1.2 Pharmacotherapy for Diabetic Painful Neuropathy

The Diabetes Control and Complication trial (DCCT) showed that in Type I diabetes (T1DM) patients intensive insulin treatment reduced the risk of developing DPN by 60% to 69%, which persisted for another 13 to 14 years,[31] yet the impact of tight glycemic control was smaller in T2DM patients.[32] The Action to Control Cardiovascular Risk and Diabetes trial randomized 10,251 T2DM patients through their HbA1c level. The intensive glycemic control group (HbA1c < 6%) reduced the annual risk of developing DSPN by 0.7%, and they reached a modest 5% reduction after 3.7 years, but the difference was not statistically significant.[33] Overall, the meta-analysis in a Cochrane review showed enhanced glucose control (more frequent subcutaneous insulin administration, continuous insulin infusion, oral antidiabetic agents, lifestyle modifications such as diet and exercise, or pancreas transplant) reduced the risk of developing clinical neuropathy by 1.84% (95% confidence interval (CI): -1.11 to -2.56) in T1DM patients; however, it was a 0.58% (95% CI: 0.01 to -1.17) risk difference in T2DM patients.[34]

Guidelines for DPN management were published in 2010 and 2011 by the International Association for the Study of Pain (IASP) Neuropathic Pain Special Interest Group (NeuPSIG),[35] the European Federation of Neurological Societies (EFNS),[36] the American Academy of Neurology (AAN),[37] the UK National Institute for Health and

Clinical Excellence (NICE),[38] and the Toronto Expert Panel on Diabetic Neuropathy (TEPDN).[39] Each guideline has its own evidence grading system. In general, NICE, NeuPSIG, and TEPDN add authors' clinical experience to their pharmacotherapy recommendations, but AAN and EFNS guidelines are based solely on evidence-based medicine.[40, 41] The AAN guideline had higher level A evidence than the EFNS guideline: the AAN guideline required at least two class 1 studies, whereas the EFNS guideline required at least one class 1 or two class 2 studies. The various guidelines were generated through different organizations and were written for different audiences. The TEPDN guideline is based on the opinioned experts in the Diabetic Neuropathy Study Group ascertained at the 2009 International Diabetic Neuropathy Symposium held in Toronto. The NICE guideline is funded by the UK NHS (National Health Service) and is written for nonspecialist providers; therefore, the cost-effectiveness for NHS is considered in NICE. The NeuPSIG guideline addresses neuropathic pain syndromes and is not specifically for DPN.

All guidelines indicate that clinicians have difficulty managing DPN in clinical practice due to the presence of co-morbidities, contraindications, the possible drug-drug interactions (DDIs),[42] and the different responses to medication.[43] The guidelines suggest that patients should be offered the available therapies in a stepwise fashion.[35, 38] If patients do not respond adequately to first-line treatment, or complain of adverse events, they may need to modify their treatment. Most guidelines recommend a TCA including nortriptyline, desipramine, or tertiary amine TCA (25-150 mg/day) or duloxetine (60-120 mg/day) as first-line agents, but the AAN choose only pregabalin (150-600 mg/day) as a first-line agent. Among the TCAs, nortriptyline and desipramine are considered the best

choice by NeuPSIG,[35] but not by NICE, which prefers amitriptyline as first-line treatment instead (Table 1.1-1.2). The recommended next steps of the guidelines are as follows: change to another first-line agent; change to a second-line agent; or add a different first- or second-line agent.[35] NICE suggests that if symptoms do not improve at the maximum tolerated dose (MTD), switch to pregabalin instead of adding it.[38] TEPDN states that if the pain is still not well-controlled, add opioids such as tramadol and oxycodone as a combination treatment.[44] EFNS recommends that if patients show partial response to drugs administered alone, use gabapentin combined with nortriptyline as the next step. [36]

In conclusion, TEDPN, NeuPSIG, EFNS, NICE, and AAN suggest gabapentinoids (e.g., pregabalin, gabapentin), tricyclic antidepressants (e.g., amitriptyline, nortriptyline, desipramine), a norepinephrine-serotonin reuptake inhibitor antidepressant (e.g., duloxetine), opioids (e.g., oxycodone, methadone, hydrocodone), and a dermal lidocaine patch as first- and second-line treatments for DPN. Among them, duloxetine and pregabalin have received U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for DPN.[44, 45] All of these medicines impact the pain pathway. Tricyclic antidepressants (TCAs) modulate the descending pain inhibition pathways of the brain stem and spinal cord primarily through inhibition of norepinephrine and serotonin reuptake, and perhaps somewhat through blockage of N-Methyl-D-Aspartate receptors, Na^+ channels, Ca^{2+} channels, α-adrenergic receptors, muscarinic-cholinergic receptors, and opioid receptors, which mediate hyperalgesia and allodynia.[46] Earlier reports suggest that the tertiary amines (amitriptyline) have balanced serotonin and norepinephrine reuptake inhibition, and may have better efficacy for DPN compared to secondary amines (nortriptyline, desipramine). However, a controlled

Table 1.1 Pharmacotherapy in DPN Guidelines

	TCAs	Duloxetine	Gabapentin	Pregabalin	Opioids	Lidocaine
TEPDN (2011)	1st line	1st line	1st line	1st line	2nd line	-
NeuPSIG (2010)	1st line (nortriptyline, desipramine)	1st line	1st line	1st line	2nd line	1st line
EFNS (2010)	1st line	1st line	1st line	1st line	2nd line	-
NICE (2010)	1st line (amitriptyline)	1st line	-	1st line	2nd line (tramadol)	-
AAN (2011)	2nd line (amitriptyline)	2nd line	2nd line	1st line	2nd line	3rd line

TEPDN: Toronto Expert Panel on Diabetic Neuropathy; NeuPIG: Neuropathic Pain Special Interest Group; EFNS: European Federation of Neurological Societies; NICE: National Institute for Health and Clinical Excellence; AAN: American Academy of Neurology

Table 1.2 Dosage Recommendation of Each Guideline

	TCAs	Duloxetine	Gabapentin	Pregabalin	Opioids	Lidocaine
TEPDN (2011)	amitriptyline (25-75 mg/d)	60-120 mg/d	900-3600mg/d	300-600 mg/d	tramadol (200-400 mg/d)	-
	imipramine (25-75 mg/d)				oxycodone (20-80 mg/d)	
					morphine sulfate SR (20-80 mg/d)	
NeuPSIG (2010)	nortriptyline (150 mg/d)	60 mg bid	1200 mg tid	200 mg tid	tramadol (400 mg/d)	3 patches /d for a max12-18 hrs
Max dose	desipramine (150 mg/d)				morphine (120-180 mg/d)	
EFNS (2010)	25-150 mg/d	60-120 mg/d	1200-3600 mg/d	150-600 mg/d	tramadol (200-400 mg/d)	
NICE (2010)	amitriptyline (75 mg/d)	120 mg/d	-	300 mg bid	-	-
AAN (2011)	amitriptyline (25-150 mg/d)	60-120mg/d	900-3600 mg/d	300-600 mg/d	tramadol (210 mg/d)	
					oxycodone (120 mg/d)	
					morphine sulfate SR (120 mg/d)	

TEPDN: Toronto Expert Panel on Diabetic Neuropathy; NeuPIG: Neuropathic Pain Special Interest Group; EFNS: European Federation of Neurological Societies; NICE: National Institute for Health and Clinical Excellence; AAN: American Academy of Neurology; bid: twice a day; tid: three times a day; SR: sustained release

clinical crossover trial conducted by Max et al. showed that the efficacy of desipramine was similar to amitriptyline.[47] Additional comparative trials would be useful to differentiate tertiary and secondary amines, but it is hard to fund trials for a generic product. The secondary amines (desipramine) are useful alternatives in patients unable to tolerate the side effects of amitriptyline, which has higher anticholinergic effects (dry mouth, constipation, and urinary retention).[48] Overall, the advantages of TCAs are once-daily dosing, low cost, and treatment of depression, which is a common co-morbidity in DPN patients. Clinical trials showed TCAs have an equivalent analgesic effect on both depressed and nondepressed patients,[49,50] and the doses of TCAs for DPN are one-half to one-third the antidepressant doses. However, TCAs should be used with caution in patients with cardiac conduction disturbances and ischemic heart disease.[43] Duloxetine (serotonin norepinepherine reuptake inhibitor (SNRI)) is an FDA-approved medication for DPN, and it has consistently demonstrated efficacy in some patients as described in systemic reviews.[43] The most common side effect of duloxetine is nausea, but if the treatment is initiated at 30mg/day and titrated up after one week to 60mg/day, the nausea occurs less frequently.[51] The advantage of duloxetine over a TCA is that there is no caution for cardiovascular patients.[52]

Gabapentin and pregabalin bind at the α_2-δ subunit voltage-gated calcium channel producing changes in neurotransmitter release, but pregabalin has a 6-fold higher binding affinity than gabapentin.[7] Pregabalin is an FDA approved medication for DPN that can be given twice daily, and the dosage can be rapidly titrated compared to gabapentin, which has complicated, nonlinear pharmacokinetics and is administered three times daily. The most common side effects for gabapentin and pregabalin are dizziness,

somnolence, peripheral edema, and dry mouth.[36] Currently, pregabalin is markedly more expensive than generic gabapentin, but the patent for pregabalin will expire in 2018 at which time generics will make it less expensive. Even though there are few drug interactions for gabapentin and pregabalin compared to TCAs, doses must be reduced in patients with renal insufficiency.[49]

Topical lidocaine and opioids are the other two first-line medications for DPN. The lidocaine patches provide local anesthesia in the outer layers of skin and muscle and are usually well tolerated with few systemic adverse effects. Typically, lidocaine patches are used when neuropathic pain is well localized.[49] Opioids provide analgesia by acting as agonists at mu and kappa opioid receptors in the central nervous system. Tramadol has different mechanisms, which include being a weak opioid and a mixed SNRI. However, morphine, oxycodone, and tramadol all have shown efficacy in DPN. The main concerns of opioids are their long-term safety, including abuse potential, immunologic changes, hypogonadism, and opioid-associated hyperalgesia.[43] The common adverse effects of opioids include respiratory depression, sedation, nausea, itching, and constipation.[49] In conclusion, opioids are unique in providing immediate pain relief compared to other medicines.

Number Needed to Treat (NNT) is an epidemiological measure used to assess the effectiveness of a healthcare intervention. The NNT provides an indirect comparison of efficacy, which is the reciprocal of the absolute risk reduction (ARR) which is the difference between the control group's event rate and the experimental group's event rate. Therefore, the ideal NNT is 1 meaning that everyone improves (≥50% pain reduction) with treatment compared to placebo. The higher the NNT, the fewer the number of

patients who will experience at least a 50% reduction in pain. Finnerup et al.[53] did a systemic review of the medications in DPN, and it showed the best medication for DPN was amitriptyline (NNT: 2.1),[50] followed by nortriptyline (NNT: 2.5), morphine (NNT: 2.5), oxycodone (NNT: 2.6), tramadol (NNT: 3.4), pregabalin (NNT:3.9),[54] gabapentin (NNT: 3.9), and duloxetine (NNT: 5.2). However, these results are different from the Cochrane reviews.[55-59] The Finnerup et al. report only includes studies published through April 2005, but the Cochrane review includes studies through 2014. The Cochrane review includes the studies in the Cochrane CENTRAL, MEDLINE, and EMBASE databases, and the authors also hand-searched unpublished data from ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform. The Cochrane review showed that duloxetine at 60 mg daily was effective in treating DPN in the short term, with a risk ratio (RR) for ≥ 50% pain reduction at 12 weeks of 1.73 (95% CI: 1.44- 2.08), and the related NNT was 5 (95% CI: 4- 7).[57] Gabapentin at 1200 mg or more daily was significantly better than placebo for at least 50% pain relief in DPN (38% vs. 21%), and the related NNT was 5.9 (95% CI: 4.6- 8.3).[59] Opioids were significantly better than placebo in treating neuropathic pain, with risk difference for ≥ 50% pain reduction of 0.17 (95% CI: 0.02-0.33, P =0.03), and the related NNT was also 5.9 but with a wider confidence interval (95% CI: 3.0-50.0).[58] Both desipramine[56] and imipramine[55] had no first- or second-tier evidence, but the third-tier evidence in individual studies indicated some improvement in pain relief with desipramine and imipramine compared with placebo. A 3-month third-party payer cost-utility analysis used decision model to estimate cost effectiveness of despramine 100mg/day, gabapentin 2400mg/day, pregabaline 300mg/day, and duloxetine 60mg/day in DPN patients, and the

result showed desipramine and duloxetine both were more effective and less costly. The incremental cost-effectiveness ratio (ICER) for duloxetine to desipramine was $US47,700 per QALY.[60]

1.3 The Inadequacy of Current Treatments

DPN patients are commonly untreated or under-treated. One UK cohort study conducted at ten outpatient pain clinics found that 79% of the neuropathic-pain patients suffered from their pain for at least one year before they visited the pain clinic.[61] Another UK study reported that only 81.4% of DPN patients (n=4,317) were treated with medication, which means 18.6% were not treated.[25] One mail-survey study used the S-LANSS questionnaire to identify neuropathic pain. Of the 4,541 returned surveys, 8.9% of the cohort had neuropathic pain (n=399). Among them, 215 patients had S-LANSS scores over 12, but 117 of them received no neuropathic pain medication.[62] That is to say, 54.4% of the neuropathic-pain patients were not treated in this study.

Admittedly, many DPN patients are unsuccessfully treated. Their pain is not well controlled even when they take the medications regularly. Mendell et al. reported that most DPN therapies produce only 30 to 50% pain reduction in 2003.[63] In one prospective study about 75% of DPN patients reported pain of the same severity after five years, which showed that their pain was not controlled.[64] One 2006 European survey reported that 82% of DPN patients had moderate or severe pain (the pain interference: 4.8±2.4), on a scale of zero to ten with zero meaning no pain and ten meaning pain as bad as the patient could imagine, while 47% of them had received the medicine for more than a year with good adherence by their own reports.[29] Torrance et al. showed that 50 of 98 treated

patients took two or more neuropathic-pain medications for at least three months, and their pain severity was still more than five. Also, ten patients had refractory neuropathic pain in that study: using four or more neuropathic medications for at least three months, poor quality of life, or having a pain severity more than five for more than six months.[62] Due to the unsuccessful treatment, patients reported disappointment in one US study: only 22.4% of DPN patients were satisfied with their medication, and only 23.1% reported it as effective.[22]

The literature also reported that physicians do not always prescribe guideline-suggested medications. The UK cohort study reported that duloxetine and venlafaxine were prescribed to fewer than two percent of DPN patients,[25] which is not consistent with the NICE and EFNS guidelines that suggest use of duloxetine as a first-line treatment.[36, 38] A US study conducted by Gore et al. reported that 46.7% of 255 patients used non-steroidal anti-inflammatory drugs (NSAIDs),[22] a medication class with no proven efficacy for DPN.

Lastly, many DPN patients stop or change their medicine, making it difficult for them to find a successful treatment. One survey reported 70% of providers prescribed medications three or more times before concluding treatment failure.[65] It is also common for patients to discontinue the treatment, switch, or add on after the initial therapy. A Swedish Registry study (n=13,479) showed that only 10 to 20% of patients remained on their neuropathic pain treatment over the three years, and half of them discontinued their treatment during the first 47-160 days.[66] About 24% of the neuropathy patients (n=2,220) received a second neuropathic-pain (Neup) drug after their first Neup drug, for which they could either switch drugs or add another on. Most of them switched to another

medicine within six months (11%), some of them switched to another medicine after six months (7.5%), and a few of them added another medication (5.4%). Pregabalin was the most common second Neup drug (31%), followed by amitriptyline (28%) and gabapentin (26%). Among non-Neup prescriptions, strong opioids (9%), NSAIDs (including aspirin), and acetaminophen (9%) were the most common drugs to be added on. Among mental-health co-medications, benzodiazepines (10%) and SSRIs (8%) were the most common drugs to be added on for neuropathic pain patients.[66]

1.4 Rationale of Combination Pharmacotherapy

Optimal combination pharmacotherapy has been defined by Gilron et al. as: "two effective analgesic drugs that have complementary analgesic actions and substantially different side-effect profiles associated with little overlap of side-effects, such that the side-effect profile is minimized and efficacy is maximized."[67] In other words, the best combinations are two medicines that result in maximal pain relief and minimal adverse effects. Mao et al. state that several types of drug combinations are currently available: "1) combination of drugs from the same drug class that differ in their pharmacokinetics (i.e., onset and duration of action), such as combination of immediate with extended release opioid analgesics, 2) combination of two or more drugs from different drug classes, such as a combination of opioid with TCA, and 3) combination of drugs delivered through different routes, such as combination of topical agent with oral agent."[68] Experts encourage DPN patients to use combination pharmacotherapy and the literature presents some rational reasons for using it: patients often cannot control their pain with mono-pharmacotherapy, fully effective analgesic pharmacotherapy for DPN remains elusive,

and most DPN patients have multiple etiologies, which require multiple medications for control.

DPN patients often do not achieve their pain control with mono-pharmacotherapy; it is therefore common to use more than one drug. In a questionnaire study conducted with 357 primary care healthcare providers in New England, it was found that 90% of the patients required two or more medications.[65] Kozma et al. using the MarketScan database reported that among 8004 patients who took pregabalin, 3,956 (49%) of them received an opioid before and after their pregabalin prescription, and 1,580 (20%) of them received an opioid only after pregabalin prescription, [69] indicating that managing DPN with pregabalin alone is insufficient. The Gore et al. study reported on how DPN patients used medication in the week preceding the survey. On average, DPN patients took 3.8 (SD=3.9) different types of prescription drugs and two OTC medications: 79.2% of them reported taking at least one prescription medication, 52.2% of them reported taking at least two, and 47.8% of them were using both prescription and OTC medications. The study also showed that the higher the pain severity, the more medicines were taken.[22] The reason for taking multiple medications is the lack of specific and selective medications to alleviate DPN, and the effectiveness is often reduced by dose-limiting side effects.[45, 70] Overall, the clinical trials have shown that the maximum response to mono-pharmacotherapy on DPN is only around 50%.

The development of fully effective analgesic pharmacotherapy for DPN remains elusive. Four main obstacles in clinical pain research have been described in the literature.[71] First, the process to determine neuropathic pain has not been standardized. Even though the neuropathic pain questionnaire, LANSS, can define the neuropathic pain,

the sensitivity (78-83%) and specificity (78-90%) of the questionnaire is not perfect.[72] Second, experiments to determine the mechanism of action for the drugs were done in animal models, but owing to interspecies differences, varying physiology, receptor distribution, and evoked responses, the result of the experiments cannot be fully applied to humans. That is to say, the pain experienced and the treatment response in animals often differs from that in humans. Third, a standardized way to collect and characterize the symptoms and the signs of each individual's pain has not been defined.[73]

A cohort study used the neuropathic pain symptom inventory (NPSI) questionnaire and quantitative sensory testing (QST) to collect the baseline responses of four neuropathic pain disorders: central post-stroke pain, post-traumatic peripheral pain, painful HIV neuropathy, and DPN. The results showed each etiology has several distinct neuropathic-pain sensory profiles.[74] One multinational randomized controlled trial (RCT) also reported that DPN patients had varying sensory profiles,[75] and the *post hoc* cluster analysis reported different sensory profiles leading to differential responses in duloxetine and pregabalin.[76] Last, the population enrolled in clinical trials is usually not the same as in the real world. The landmark Institute of Medicine (IOM) report, *Relieving Pain in America*, addressed the fact that RCTs may not be the most appropriate way to evaluate new analgesic agents, because RCTs have detailed requirements for their study population; however, chronic-pain patients have diverse biological, psychological, demographic, social clinical characteristics.[77] RCTs also often exclude elderly patients and those with co-morbid psychological disorders, multiple pain disorders, or those taking other pain medications. Furthermore, the time frame of RCTs is usually 4 to 14 weeks, which is much shorter than the lifetime treatment for DPN. As a result, some

medicines that show efficacy in RCTs do not show effectiveness in the real world.

Because DPN patients have more than one etiology, they will require more than one medicine to control it. Even though the fundamental etiology has not been determined, the symptom complex of DPN patients demonstrates that in order to treat the whole person, medicine needs to be prescribed in various ways; instead of a single approach, a personalized approach is required. Based on the pharmacology and mechanism approach, combination pharmacotherapy is rational. The treatment of neuropathic pain could include: (1) sodium channel blockers to reduce spontaneous and ectopic activity (e.g., lidocaine), (2) specific calcium channel blockers to counter nerve injury–induced changes in calcium channel subunit function (e.g., gabapentin, pregabalin), (3) SNRIs to facilitate endogenous antinociceptive signaling, and (4) minocycline to attenuate experimental pronociceptive microglial activation. Combination pharmacotherapy for pain management is recommended in the guidelines from the World Health Organization (WHO),[78] American Pain Society (APS), and American College of Rheumatology (ACR). Also, an American Academy of Family Physicians (AAFP) report advocated that many neuropathic-pain patients will require rational combination pharmacotherapy to obtain pain relief.[79]

Sequential treatment is commonly used in clinical practice, but it restricts exposure of patients to more than one drug initially and limits combination pharmacotherapy.[80] One study showed that the sequential addition of oxycodone safely reduced neuropathic pain in DPN patients who were initially treated at the maximum tolerated dose (MTD) of gabapentin.[81] Even though it is effective to use sequential treatment, there is an advantage to concurrent treatment. Concurrent treatment allows

simultaneous titration of two drugs. Although it is not possible to know which medicine is more effective, concurrent treatment (combination pharmacotherapy) has shown efficacy in treating DPN patients in RCTs. In a double blind, crossover trial, DPN and postherpetic neuralgia (PHN) patients had better pain relief with combination treatment than just gabapentin or nortriptyline alone.[82] In another RCT, DPN or PHN patients also reported better pain relief with a gabapentin-morphine combination than either as a single agent, but the MTD of the gabapentin-morphine combination was also lower.[83] A meta-analysis involving 386 participants from two studies[81, 83] demonstrated a statistically significant superiority of gabapentin plus opioid over gabapentin alone, but with more frequent side effects than with gabapentin alone.[84]

1.5 Gaps in the Evidence for Combination Pharmacotherapy with DPN Patients

Even though at least 45% of the DPN patients used more than one medicine in clinical practice,[85] only a few combination pharmacotherapy clinical trials have been published (Table 1.3). A Cochrane review that assessed combination pharmacotherapy in neuropathic pain only identified 11 high-quality randomized controlled trials (RCT) for DPN.[81-84, 86-92] Most trials showed better efficacy with combination pharmacotherapy, but one RCT in patients with PHN or DPN did not detect a statistically significant difference between pregabalin-oxycodone (10mg/ day) combination and pregabalin alone. The reason might be that the mean duration of diabetes was longer in the pregabalin-oxycodone combination than in the pregabalin group (4.5 years vs. 2.9 years), there were fewer females in the pregabalin-oxycodone group (33% vs. 52%), and the literature reports that females are associated with a stronger placebo effect than males.[92] A

Table 1.3 Combination Pharmacotherapy Studies in DPN

First Author, Year	Study Period	Disease	T1	T2	T3	T4	Titration of fixed dosage	Pain Measurement/ Mean changes in pain relief	Key Outcomes
Zin 2010[92]	6 weeks	DPN (n=30) PHN (n=32)	Pre + Oxy	Pre + Plc			Pre: 75-600mg Oxy:10mg	VAS/ 3.6 vs. 4.0 (p=0.07)	Mean changes in pain relief; 50% pain reduction ; SF36; PGIC; AE
Gilron 2005[83]	6 weeks	DPN (n=35) PHN (n=22)	Gab + Mor	Mor	Gab	Plc	Mor: 60-120mg Gab: 2400-3200mg	MPQ, NRS/ 2.4 vs. 1.7 vs. 1.5 vs. 1.1	Mean changes in pain relief; SF36; BPI; PGIC; AE
Gilron 2009[82]	6 weeks	DPN (n=40) PHN (n=16)	Gab+ Nort	Gab	Nort		Gab: 3600 mg Nort: 100 mg	NRS/ 2.4 vs. 1.6 vs. 1.8	Mean changes in pain relief; SF36; BPI; PGIC; AE
Freeman 2007[87]	66 days	DPN (n=313)	Tramadol/APAP	Plc			Tramadol: 37.5 mg APAP: 325 mg	NRS/ 2.7 vs. -1.8 (p=0.001)	Mean changes in pain relief; PGIC; AE
Tesfaye 2013[75]	12 weeks	DPN (n=804)	Dul+ Pre	Dul	Pre+ Dul	Pre	Dul: 60-120mg Pre: 300-600mg	BPI-MSF/ 2.35 vs. 2.16 (p=0.370)	Mean changes in pain relief; 50% pain reduction ; PGIC; AE
Agrawal 2009[86]	12 weeks	DPN (n=83)	GTN spray + Na. Val	GTN spray + Plc	Plc spray+ Na. Val	Plc spray + Plc	GTN: 0.4mg Na. Val: 20mg/kg	VAS/ 2.5 vs. 2.8 vs. 1.85 vs.0.45	Mean changes in pain relief; SF-MPQ;

† MPQ: McGill Pain Questionnaire; VAS: Visual analog scales; BPI-MSF: Brief Pain Inventory Modified Short Form; SF 36: Short form 36; PGIC: Patient global impression of change; NRS: Numerical Rating Scale; BS-11: Box Scale-11; AE: adverse events; Gab: gabapentin; Nort: nortriptyline; GTN: glyceryl trinitrate; APAP: acetaminophen; Mor: morphine; Oxy: oxycodone; Pre: pregabalin; Dul: duloxetine; Plc: placebo; Na.: Sodium; Val: valproate; T1: Treatment1

multicenter RCT did not show a statistically significantly difference in pain reduction between a duloxetine (60mg/day)-pregabalin (300mg/ day) combination and high-dose monotherapy (p=0.370); however, the duloxetine-pregabalin combination had better scores in the mean changes in pain relief and 50% pain reduction, and it is considered to be effective, safe, and well tolerated.[75] Many experts, and the guidelines, recommend doing more clinical trials on combination pharmacotherapy to examine the safety and

efficacy of different regimens.[68]

A systematic review conducted by Gilron et al. suggested the need for future combination pharmacotherapy studies, in order to understand the pharmacokinetics and pharmacodynamic interactions between components of analgesic combinations, and to define the optimum dose ratio between components.[67] Furthermore, Gilron et al. suggested improved methods of assessing the interaction of multiple concurrent analgesic drugs and their side effects.[67] Because most combination pharmacotherapy studies only compare a combination of drugs (A+B) with one drug (e.g., A); it is necessary to incorporate the additional comparison of A+B with B alone to make the evaluation more complete and useful.[67] For example, the study conducted by Agrawal et al. had four comparison groups: glycerol trinitate (GTN) spray/sodium valproate, GTN spray/placebo, placebo spray/sodium valproate, placebo spray/placebo, which showed the complete comparison between combination pharmacotherapy and mono-pharmacotherapy.[86] However, the study conducted by Freeman et al. only compared tramadol/acetaminophen with placebo,[87] and although the reduced daily pain was statistically significant ($p=0.001$) between tramadol/acetaminophen and placebo, the effect of the tramadol or acetaminophen was not been examined in this study.

No published observational studies have compared combination pharmacotherapy with mono-pharmacotherapy in DPN patients. To date, comparisons between combination pharmacotherapy and mono-pharmacotherapy have only included RCTs. However, there are some observational studies that compared medication usage, clinical characteristics, co-morbidities, and healthcare costs with different DPN medications (Table 1.4).[21, 69, 93-103]

Table 1.4 Observational Studies in DPN

First Author, Year	Database	Study Time	Study Population	All costs (Cost Difference)	Outcomes	Funding
Gore, 2011[93]	Pharmetrics	1/1/2004-12/31/2005	Pregabalin (n=1178)	$ 31,567 ($4,796)	Comorbidities Pain-related pharmacotherapy Health resource utilization Direct Medical costs	Pfizer
		pre-index: 1 year	Gabapentin (n=1178)	$ 33,360 ($6,334)		
		post-index: 1 year				
Gore, 2011[21]	Pharmetrics	1/1/2004-12/31/2005	Pregabalin (n=713)	$ 30,914 ($6,042)	Comorbidities Pain-related pharmacotherapy Health resource utilization Direct Medical costs	Pfizer
		pre-index: 1 year	Duloxetine (n=713)	$ 30,881 ($2,691)		
		post-index: 1 year				
Zhao, 2010[94]	MarketScan	3/1/2004-12/31/2005	Duloxetine-continuous† (n=98)	$ 31,898 (2,732)	Comorbidities Pain-related pharmacotherapy Changes in Opioid use Direct Medical costs	Eli Lilly
			Duloxetine- non-continuous(n=243)	$ 43,796 (8,298)		
		pre-index: 1 year	SOC‡-continuous (n=195)	$ 34,934 (-$10,701)		
		post-index: 1 year	SOC- non-continuous(n=745)	$ 40,634 (800)		
Wu, 2011[95]	MarketScan	3/1/2004-12/31/2005	Duloxetine (n=272)	$ 25,466 ($3,463)	Comorbidities Pain-related pharmacotherapy Direct Medical costs	Eli Lilly
		pre-index: 1 year	SOC (n=227)	$ 37,524 ($1,685)		
		post-index: 1 year				
Chen, 2010[96]	MarketScan	3/1/2004-12/31/2005	Duloxetine (n=117)	$ 18,623 ($-3,632)	Comorbidities Pain-related pharmacotherapy Health resource utilization Direct Medical costs	Eli Lilly
		pre-index: 1 year	SOC (n=117)	$ 30,602 ($8,896)		
		post-index: 1 year				
Chen, 2011[97]	MarketScan	7/1/2004-12/31/2007	Duloxetine (n=1123)	$ 30,852*	Comorbidities Pain-related pharmacotherapy Health resource utilization Direct Medical costs	Eli Lilly
			TCAs (n=1528)	$ 29,313*		
			Venlafaxine (n=500)	$ 33,585*		
			Gabapentin (n=3655)	$ 39,012*		
		pre-index: 1 year	Pregabalin (n=2207)	$ 33,284*		
		post-index: 1 year	Opioids (n=2047)	$ 39,265*		

*pre-index costs

Table 1.4 Continued

First Author, Year	Database	Study Time	Study Population	All costs (Cost Difference)	Outcomes	Funding
Zhao, 2011[98]	MarketScan	1/1/2005-1/1/2007	Duloxetine (n=794)	$ 34,188 ($ 9,315)	Comorbidities Medication adherence Direct Medical costs	Eli Lilly
		pre-index: 1 year	Pregabalin (n=1779)	$ 34,710 ($ 9,906)		
		post-index: 1 year				
Burke, 2012[99]	MarketScan	9/1/2005-6/30/2009	Pregabalin (n=1785)	$ 15,420 ($1,411)	Comorbidities Health resource utilization Direct Medical costs Medication Adherence	Pfizer
		pre-index: 6 months	Duloxetine (n=351)	$ 12,540 ($1,560)		
		post-index: 6 months				
Margolis, 2010[100]	MarketScan	10/1/2005-3/1/2009	Pregabalin (n=473)	$ 14,885 ($2,239)	Comorbidities Pain-related pharmacotherapy Health resource utilization Direct Medical costs	Pfizer
		pre-index: 6 months	Duloxetine (n=473)	$ 13,680 ($3,337)		
		post-index: 6 months				
Udall, 2012[101]	MarketScan	1/1/2007-12/31/2008	Pregabalin (n=910)	$ 24,754 ($ 3,081)	Comorbidities Pain-related pharmacotherapy Health resource utilization Direct Medical costs	Pfizer
		pre-index: 1 year	Gabapentin (n=910)	$ 27,870 ($ 4,684)		
		post-index: 1 year				
Udall, 2012[102]	MarketScan	1/1/2007-6/30/2009	Pregabalin (n=987)	NA	Medication Adherence Direct Medical costs	Pfizer
			Duloxetine (n=349)			
		pre-index: 1 year	Gabapentin (n=987)			
		post-index: 1 year	Amitriptyline (n=276)			
Johnston, 2013[103]	MarketScan	7/1/2007-3/30/2011	Duloxetine (n=1354)	$ 27,331 (NA)	Comorbidities drug-drug interactions drug-condition interactions	Pfizer
		pre-index: 6 months	Pregabalin (n=2499)	$ 20,736 (NA)		
		post-index: 6 months				

† Continuous: Medication Possession Ratio (MPR)≥ 80%

‡SOC: TCAs, Venlafaxine, gabapentin, pregabalin

Three pharmaceutical industry-funded studies found that DPN patients who were initiated on duloxetine were less likely to have subsequent opioid use than standard care (TCAs, venlafaxine, gabapentin, and pregabalin).[94-96] However, Margolis et al. had different findings: patients who initiated therapy with duloxetine or pregabalin had no significant difference in DPN-related analgesic medications.[100] Because different pharmaceutical industry-funded studies showed different results, there may be a conflict of interest. However, all studies showed substantial medication burden and co-morbidities in DPN patients, including musculoskeletal and neuropathic pain conditions.

Most studies found that immediate-release opioids and NSAIDs were the most commonly prescribed medications after the first-line DPN medications.[95-97, 104] Several studies compared healthcare costs of different first-line treatments. Gore et al.[21] used Pharmetrics and Udall et al.[101] used the MarketScan database to compare pregabalin with gabapentin, and both studies showed no statistically significant difference in all-cause costs.[21, 101] However, Gore et al. reported greater pain-medication burdens with gabapentin than pregabalin,[21] and Udall et al. observed the higher prescription costs in pregabalin than gabapentin.[101] Again Gore et al.[93] used Pharmetrics, and Burke et al.,[99] and Margolis et al.[100] used MarketScan to compare pregabalin with duloxetine, and all studies showed no statistically significant difference in all-cause costs.[93, 99, 100] However, Gore et al. found that there were higher medication costs with duloxetine than pregabalin.[93] Zhao et al.,[94] Wu et al.,[95] and Chen et al.[96] used MarketScan to compare duloxetine with standard of care (SOC), which as TCAs, venlafaxine, gabapentin, and pregabalin. All studies found that patients who initiated therapy with duloxetine had better adherence than SOC, and the better adherence led to lower healthcare costs.[94-96]

In conclusion, the all-cause cost is not statistically significantly different if only comparing a first-line agent with another first-line agent. Only one study compared the DDI costs between duloxetine and pregabalin; Johnston et al. used MicroMedex to measure DDIs and used the Contraindications and Warnings and Precautions sections to define drug-condition interactions (DCIs). Their result showed duloxetine users had higher DDI and DCI costs than pregabalin users[103] (Table 1.4).

Overall, even though it is essential to know the relationships between medications and the clinical characteristics or healthcare costs in DPN patients, evidence is lacking to provide an understanding of the relationships between combination pharmacotherapy and its treatment patterns, co-morbidities, and healthcare costs in DPN patients.

1.6 Current Reimbursement for DPN Medications

A web-based survey of 300 physicians reported that nearly one-third of doctors did not receive sufficient reimbursement for their diabetic care, and 83% of them reported that Medicaid reimbursement was inadequate, while 67% reported private insurance reimbursement was inadequate.[105] Leichter et al. concluded that the current system rewards less-excellent providers and penalizes more-excellent ones, which means many insurers may attempt to "downcode" the corrected coding for diabetic care or audit the frequency with which individual providers bill at a high level of service.

Not only is there a reimbursement hurdle, but there are also prescribing restrictions through either a prior authorization requirement or step therapy. Margolis et al. concluded that prior authorization (PA) was shown to effectively control access to pregabalin in both Medicaid and commercial health plan populations.[106, 107] For the

Medicaid population, the restricted states included one large industrial state and one smaller rural state. The unrestricted states included two large industrial states and two smaller rural states. The PA in the Medicaid population study was associated with increased opioid use and significantly greater disease-specific costs.[106] For the commercial health plans population, the restriction was shown to have no statistically significant differences in the use of nonpregablin medications, and there was no between-group difference in disease-related healthcare costs.[107] Suehs et al. examined the impact of the step therapy policy for pregabalin implemented by a large national health insurance provider, Humana, Inc. The restricted cohort demonstrated greater decrease in pregabalin utilization and increase in gabapentin utilization compared with the unrestricted cohort.[108] The three studies demonstrated that both PA and step therapy have impacts on the usage of pregabalin.

The NICE guideline includes a cost-effectiveness Markov model to determine first-line treatment. The Markov model was based on two pain states: at least 50% pain reduction, or no pain reduction. For patients who experienced pain relief, they were assumed to remain on the drug and continue to get pain relief for the remainder of their lifetime. For patients who experienced pain relief and minor adverse events, they were assumed to have been titrated to the minimum dose that gives pain relief and would continue to experience the adverse events or require drugs to alleviate them for their lifetime. The compliance was assumed to be 100% at base case, but was lowered to 50% in sensitivity analysis. The resource use was estimated through expert opinion. In the model presented it is recommended to use duloxetine 60 mg/day and amitriptyline 75 mg/day in both base case and probabilistic sensitivity analysis. However, it is preferable

to use amitriptyline 75 mg/day when the willingness-to-pay (WTP) is £20,000.

Mack et al. did a systemic review on the off-label use of gabapentin for DPN, and summarized that there are solid research reports on gabapentin usage, the fact that the FDA has not approved this drug for this usage should not affect health insurance companies paying for it.[109] In the range of prices for DPN medications, according to Drugstore.com, pregabalin is the most expensive at $189.98 per month, followed by duloxetine at $170.99 per month. In contrast, gabapentin comes in at $18.99 per month, amitriptyline at $12.99 per month, and nortriptyline at $19.99 per month. Due to the fact that effectiveness of the DPN medications do not differ much, it is reasonable to start with a less expensive one. However, TEPDN,[39] NeuPSIG,[35] EFNS[36] recommend both gabapentin and pregabalin as first-line, and NICE[38] and AAN[37] recommend using pregabalin but gabapentin as first-line.

1.7 Objectives of the Study

This study has the following objectives:

1. Quantify and describe newly-treated DPN treatment patterns, including which drugs were selected and in what sequence, discontinuation rates, and a count of the total classes of DPN medications used in the study period. Determine the types of combination pharmacotherapy in DPN among newly-treated patients.
2. Describe the co-morbidities by mono-pharmacotherapy DPN patients and combination pharmacotherapy DPN patients.
3. Determine predictors that newly-treated DPN patients will receive combination pharmacotherapy.

4. Compare healthcare costs between patients taking mono-pharmacotherapy and combination pharmacotherapy for DPN.

This study has the following hypotheses:

1 Patients who take combination pharmacotherapy for DPN are less likely to discontinue, switch, or add on therapy than patients who take mono-pharmacotherapy.

2 People who take combination pharmacotherapy for DPN have more co-morbidities than patients who take mono-pharmacotherapy.

3 Demographics and clinical characteristics of DPN patients will affect the likelihood of receiving combination pharmacotherapy.

4 DPN patients taking combination pharmacotherapy have lower medical costs than patients who take mono-pharmacotherapy.

1.8 Significance of the Work

As Torrance et al. reported, many neuropathic pain patients are untreated, under-treated, or unsuccessfully treated.[62] Among the different difficulties of managing DPN patients, this study focuses on the treated patients and guideline-suggested medication: to define the characteristics and optimal combination pharmacotherapy for newly-treated patients with DPN.

Some guidelines conclude that it is insufficient to use mono-pharmacotherapy to treat DPN patients and recommend prescribing combination pharmacotherapy after the failure of the first treatment. However, there is limited evidence in RCTs and no evidence in observational studies evaluating either generic product comparison or the use of

combination pharmacotherapy in DPN patients. Many questions are unanswered in this area: how many newly-treated DPN patients start with combination pharmacotherapy? What kind of newly-treated DPN patients will start with combination pharmacotherapy? What regimens do newly-treated DPN patients take? What medications are added-on or switched after the index medicine? How do the patient characteristics affect the treatment patterns, and how do the treatment patterns affect the healthcare costs? To answer those questions, the Inovalon database has been chosen as the study database. It is an innovative database that has not typically been used for this type of research. A detailed description of Inovalon is described in section 2.1.

To identify the characteristics and optimal combination pharmacotherapy in newly-treated DPN patients, the hypothesis is made that patients who receive combination pharmacotherapy will have lower healthcare costs than patients who receive mono-pharmacotherapy. This also implies that to take combination pharmacotherapy initially will be more effective in terms of not changing treatment patterns for newly-treated DPN patients.

CHAPTER 2

METHODS

2.1 Data Sources

Inovalon was selected as the data source for this project. Inovalon is a healthcare technology company founded in 1998, and per year it is responsible for over 800 Healthcare Effectiveness Data and Information Set (HEDIS) reports, which are a standardized set of performance measurements developed by the National Committee for Quality Assurance (NCQA) to evaluate consumer healthcare. For example, for comprehensive diabetes care, if the organization used correct diagnosis and procedure codes, submitted claims and encounter data in a timely manner, had the lab values (LDL, HbA1C, microalbuminuria) complete, the HEDIS score would be higher. Therefore, through the collection of the HEDIS reports, Inovalon has its own registry called Medical Outcomes Research for Effectiveness and Economics Registry ($MORE^2$). In this registry there are 5.5 billion medical data events, 78 million unique members, 1,488,974 T1DM patients, and 6,977,181 T2DM patients. All the information is divided into five databases: patient demographics, claim diagnostic data, eligibility and enrollment data, pharmacy data, and cost data (Table 2.1).

Since data collection in Inovalon was for HEDIS, some data were only available on a subset of the population. For example, there was only 30% of the cost data in our

Table 2.1 Data Dictionary

Demographic		
Field Name	Data Type	Nullable
Member ID	Integer	Not null
DOB	Date	Not null
Sex	Character varying (1)	Not null
State	Character varying (2)	Null
Zip	Character varying (9)	Not null
RaceType	Character varying (2)	Null
EthnictyType	Character varying (2)	Null
Pharmacy		
Field Name	Data Type	Nullable
Claim ID	Bigint	Not null
InferredPersonID	Integer	Not null
InferredProviderID	Integer	Not null
Claim Status	Character varying (1)	Null
FillDate	Date	Null
FillDateThru	Date	Null
NDC	Character varying (20)	Null
NDC9	Character varying (20)	Null
DaysSupply	Integer	Not null
SupplyFlag	Boolean	Not null
Billed	Numeric (19,4)	Null
Allowed	Numeric (19,4)	Null
Copay	Numeric (19,4)	Null
Paid	Numeric (19,4)	Null
Cost	Numeric 19,4)	Null
QuantityDispensed	Character varying (50)	Null
Claim diagnostic code		
Field Name	Data Type	Nullable
InferredPersonID	Integer	Not null
DOS	Date	Not null
DOSThru	Date	Null
Claim ID	Bigint	Not null
CodeType	Character varying (100)	Not null
OrdinalPosition	Smallint	Not null
CodeValue	Character varying (100)	Not null
Enrollment		
Field Name	Data Type	Nullable
InferredPersonID	Integer	Not null
EnrollmentID	Bigint	Not null

Table 2.1 Continued

Enrollment		
NewEffective Date	Date	Not null
NewTermination Date	Date	Not null
PlanEmployeeFlag (Medical Flag)	Boolean	Not null
RxFlag (Rx Indicator)	Boolean	Not null
NewPayerCode	Integer	Null
NewProductCode	Integer	Null
Claim cost		
ClaimID	Bigint	Not null
InferredPersonID	Integer	Not null
InferredProviderID	Integer	Not null
ClaimStatus	Character varying (1)	Null
Dos	Date	Not null
Dosthru	Date	Not null
Billed	Numeric (19,4)	Null
Allowed	Numeric (19,4)	Null
Copay	Numeric (19,4)	Null
Paid	Numeric (19,4)	Null
Cost	Numeric (19,4)	Null
DischargeStatus	Character varying (2)	Not null
Unitsofservice	Integer	Not null
RxProviderFlag	Boolean	Not null
PCPFlag	Boolean	Not null
RoomBoardFlag	Boolean	Not null
MajorSurgery	Boolean	Not null
ExcludeFromDischarge Indicator	Boolean	Not null
Daysdenied	Integer	Null

study, and the HbA1c value was available for only 28% of the patients, which meant the identification of the diabetes was based on the diagnostic codes, not lab values, and the study could not stratify patients by HbA1c. Table 2.1 shows the characteristics and the missing conditions in each variable. If there is “null” in the “Nullable” column, it means the variable may be missing data; if there is “not null” it means the variable must include the data.

The objectives of this study as discussed in detail in section 1.6 are to describe how the patient characteristics affect the treatment patterns, and how the treatment patterns affect the healthcare costs in DPN patients; therefore, prescriptions, co-morbidities, and cost are the three main variables in the study. Inovalon includes all of these variables including prescription data for each patient, with National Drug Code (NDC) codes and prescription filled date, allowing us to define the treatment patterns and the time to discontinue, switch, or add on to the treatment. It also has ICD9 codes for me to identify the co-morbidities of DPN, and data on the cost enabling us to calculate the healthcare costs between different treatment groups.

Other than the Inovalon database, the following sources of data were considered: 1) electronic medical records (EMR), 2) administrative claims, 3) integrated health systems, 4) national surveys, and 5) patient registries.[110] Since treatment patterns and healthcare costs are the main outcomes in the study, an EMR without these two variables was not considered. For example, if patients move to a new location or switch to a new healthcare provider, the follow-up of the medications will not be continued, which is especially an issue with chronic pain patients who change providers often; therefore, it is problematic to track the medication data and the treatment patterns in EMR.

Even though cost data are rich in administrative claim databases which are generated from providers' and patients' transactions with payers, accessing administrative claim databases costs around $60,000 to $80,000 and lower-cost options for unfunded projects involve an application process that is usually 1 year, well outside the timeline for this PhD dissertation. Another source considered was using integrated health systems, which has comprehensive data for patients with health plan coverage, as

it combines the completeness and economic data of a claim data set with the rich clinical data found in an EMR. An example is the Veterans Health Administration (VA), but the population in the VA is not generalizable to the general population, and it would be in conflict with the objectives of the study, which is to look not only at veterans but the broader US population.

The last source considered was using national surveys: the National Health Interview Survey (NHIS), and the National Health and Nutrition Examination Survey (NHANES) are examples. However, they do not have enough pain-related information. According to the questionnaire, the pain in the surveys is not stratified to acute, chronic, or persistent pain; therefore, it is hard to identify DPN patients in the surveys.

Due to the considerations of each source, the Inovalon database became the most suitable choice for this dissertation.

2.2 Study Subjects and Eligibility Criteria

2.2.1 Identify DPN Patients

The analysis period was from January 1, 2006 to December 31, 2013. The index date was the date of the first prescription filled for a DPN drug: duloxetine, pregabalin, gabapentin, TCAs (amitriptyline, desipramine, nortriptyline), opioids (tramadol, oxycodone, morphine, oxymorphone, methadone, levorphanol, hydrocodone, hydromorphone), or any route lidocaine (Table 2.2). All medications were identified through NDC codes, and to be qualified as included prescriptions, each DPN medication had at least a minimum of a 60-day supply dispensed during the post-index period, and it could be either a prescription written for 30 days with at least one refill or a prescription

Table 2.2 Medications Used for Managing DPN

Class	Individual agents
SNRI (serotonin norepinephrine reuptake inhibitors)	Duloxetine (Cymbalta)
α2δ ligands (modulate voltage-gated calcium channels)	Pregabalin (Lyrica), Gabapentin (Neurontin)
TCAs (tricyclic antidepressants)	Tertiary: amitriptyline (generic); secondary: desipramine (generic) and nortriptyline (generic)
Opioids (act on μ receptors)	Tramadol† (Ultram), oxycodone, morphine (generic), oxymorphone, methadone (Dolophine, Methadose), levorphanol (Levo-Dromoran), hydrocodone (in Vicodin, Lortab, etc.) hydromorphone (Dilaudid)
Topical agents	lidocaine patches (Lidoderm)
*Individual agents are listed alphabetically. SNRI = serotonin-norepinephrine reuptake inhibitors; TCAs = tricyclic antidepressants.	
†Tramadol also weakly inhibits serotonin and norepinephrine reuptake.	

written for 60 days, and are determined by the "DaysSupply" variable.

Patients who initiated these DPN medications between July 1, 2006 and December 31, 2012 were identified. However, patients may have used these medications before January 1, 2006, but since it is not within the study period, these data cannot be examined. Selected patients were ≥18 years old (as of the index date), had continuous health plan enrollment during the 6 months before and 12 months after the index date (pre- and post-index), and had one or more medical service claims with an associated diagnosis code for 'diabetes with neurological manifestations' (ICD-9 CM 250.6x) or 'polyneuropathy in diabetes' (ICD9-CM 357.2x) in the period 6 months prior to or up to the index date. Patients who died within a year after index date were excluded (Figure 2.1).

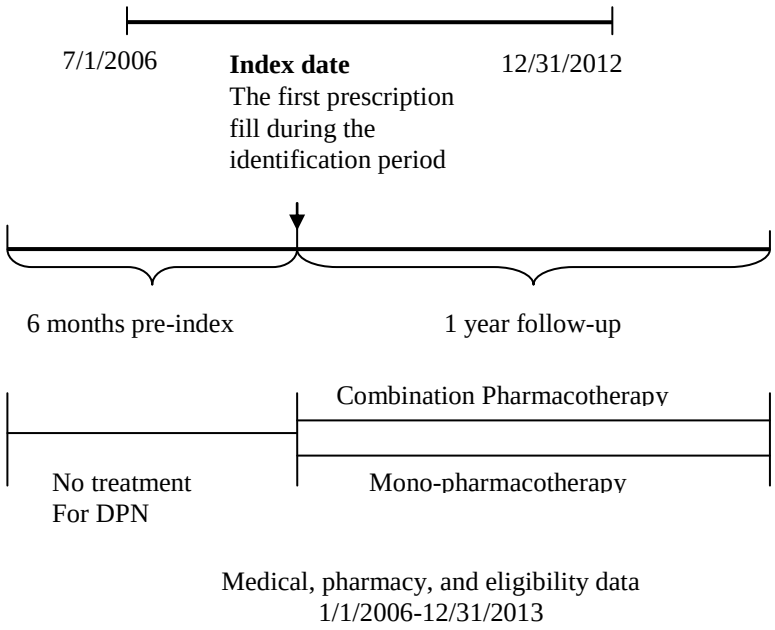


Figure 2.1 Study Time Frame Definitions

Patients were excluded from the analysis if they had a diagnosis for postherpetic neuralgia (PHN) (ICD9: 053.1X), fibromyalgia (ICD9: 729.1X), cancer (140.xx-172.xx, 174.xx-208.xx, 235.xx-239.xx), post-trauma (ICD9: 338.11, 338.21), and postoperative disease (ICD9: 338.12, 338.22, 338.18, 338.28) at any time in the available data (because these patients might have received any of the DPN medications due to their non-DPN neuropathic pain). Patients were also excluded from the analysis if they were less than 18 years of age on the index date, had no valid gender information recorded, or had any quantity of days' supply for DPN medication claims that was negative or missing.

2.2.2 Quantify Treatment Patterns

This study evaluated DPN therapies with the following drugs: TCAs (amitriptyline, desipramine, nortriptyline), opioids (tramadol, oxycodone, morphine,

oxymorphone, methadone, levorphanol, hydrocodone, hydromorphone), duloxetine, gabapentin, pregabalin, any route lidocaine, and the combinations of these drugs. In order to simplify the description for this dissertation, opioids are counted as one agent, and TCAs are also counted as one agent. Every patient in the study cohort was a newly-treated patient; none of them had any study medicine prescriptions between 1/1/2006-6/30/2006 or 6 months before the index date. The index date was defined by the first date documented as using any of the study medicine, and the medicine used on the index date would be the index medicine. There were four treatment groups in this study: discontinue, nonswitch, switch, and add-on. Every group was mutually exclusive, and Figure 2.2 is the algorithm of defining treatment groups.

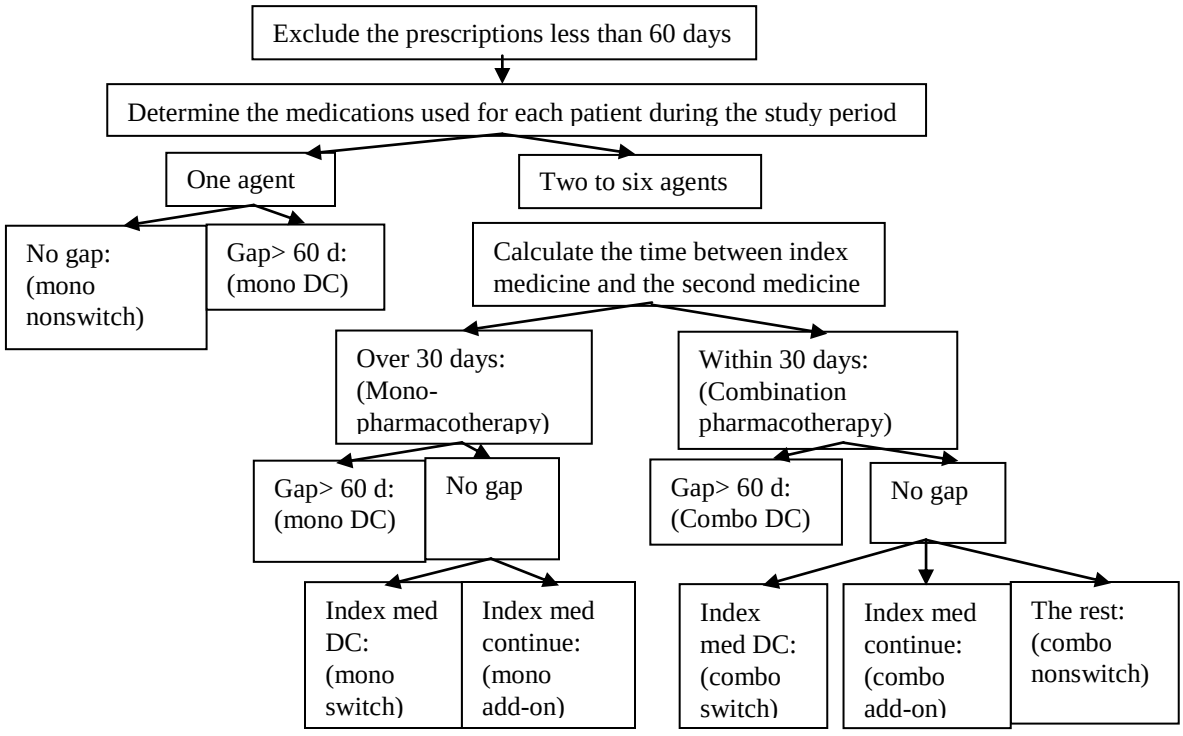


Figure 2.2 The Algorithm for Defining Treatment Groups
DC: discontinue; mono: mono-pharmacotherapy; combo: combination pharmacotherapy; med: medicine; d: days

Each group was defined as follows:

1. Exclude the prescriptions less than 60 days.

   Each medicine needed to be taken at least 60 days to be included, since treatment for less than 60 days would not have a meaningful impact on the disease; this followed the criteria defined by Romanelli et al., who conducted a study to evaluate the medication compliance for patients who started with branded statins, and the prescriptions had to have at least two pharmacy claims to be included,[111] which is a reasonable criterion for a chronic disease. Admittedly, Ziegler et al. concluded that the efficacy of DPN medication should be judged only after 2-4 weeks of treatment.[7] Even though excluding the prescriptions less than 60 days in duration will inevitably exclude some patients who do no not have prescriptions longer than 60 days, in order to determine the optimal pharmacotherapy for DPN patients, the treatment needs to be at least long enough for possible efficacy. Therefore, any records with prescriptions of less than 60 days were excluded from this study.

2. Determine the medications used for each patient during the study period.

   Patients could take TCAs, opioids, duloxetine, gabapentin, pregabalin, or any route lidocaine during the study period, or they might take any combination of two or more medicines during the study period. Determining the medications used for each patient during the study period was the first step to categorize the treatment group. There are eight treatment groups in this study: mono-pharmacotherapy (nonswitch), mono-pharmacotherapy (discontinue), mono-pharmacotherapy (switch), mono-pharmacotherapy (add-on), combination

pharmacotherapy (nonswitch), combination pharmacotherapy (discontinue), combination pharmacotherapy (switch), combination pharmacotherapy (add-on). If patients only took one medication through the study period, they were placed either into mono-pharmacotherapy (nonswitch) or mono-pharmacotherapy (discontinue). If patients took two or more medications during the study period, they were grouped into other treatment groups. Therefore, patients who only used one medication during the study period without any treatment gaps were categorized into mono-pharmacotherapy (nonswitch). For example:

a. The patient started using pregabalin from 9/25 till 2/2, and the prescription details are the following: 25Sep2007-25Oct2007; 27Oct2007-26Nov2007, 03Dec2007-02Jan2008; 03Jan2008-02Feb2008.

Mono–pharmacotherapy (nonswitch)

Therapy A					
Pre	Pre	Pre	Pre	Pre	Pre
Sep	Oct	Nov	Dec	Jan	Feb

3. Calculate the time between index medicine and the second medicine for patients with more than one medicine.

In order to define the combination pharmacotherapy, the next step was calculating the time between index medicine and the second medicine. If the time between the second medicine and index medicine was within 30 days, then it was counted as combination pharmacotherapy. If the time between the second medicine and index medicine was longer than 30 days, then it was

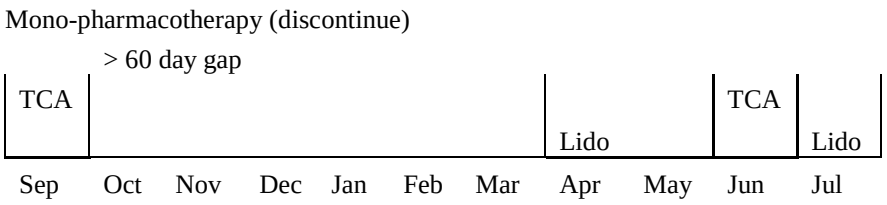
counted as mono-pharmacotherapy. Therefore, the combination pharmacotherapy is defined as having two or more medications used within the first 30 days—not the entire study period. The reason for the restriction to the first 30 days is that the objective of this study is to determine the differences between combination and mono-pharmacotherapy in time to discontinue, switch, or add on. Therefore, the combination pharmacotherapy group needs to be defined during the index period. The study conducted by Suh et al. defined combination therapy as allowing a 15-day maximum interval between a statin fill and fibrate fill.[112] However, considering the clinical aspect of DPN treatment as Ziegler et al. recommended that the efficacy of DPN medication should be judged after 2-4 weeks, for this study the interval was changed to 30 days. If patients were on combination pharmacotherapy, their index medicine would change to the combination, which means the index medicine could be, for example, gabapentin and opioids, or gabapentin and TCAs.

4. Define the discontinue groups.

   Patients would either have treatment gaps of their index medicine or not. Therefore, after defining patients on mono- or combination pharmacotherapy, the discontinue group is defined. Patients with a gap greater than 60 days during the study period would be defined as a discontinuation, and were classified into the discontinue group. Regardless of the subsequent drug therapy, if the patients had a 60-day gap of their index medicine, they would be placed into the discontinue group. The reason for choosing 60 days as a cut-off is from the Gore et al. study.[113] Gore et al. evaluated therapy switching,

augmentation, and discontinuation of the treatment in patients with osteoarthritis and chronic low back pain, and the index therapy discontinuation was defined as a gap of over or equal to 60 days between the end of the previous prescription and the start of the next prescription.[113] Therefore, if patients have a 60-day treatment gap of their index medicine, they will be placed into the discontinue group. Following are some examples:

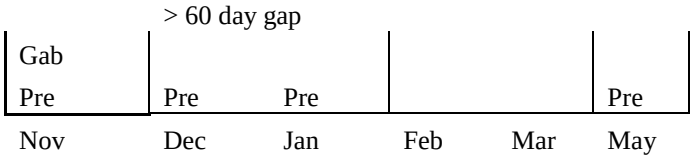
a. Patients who took one agent in the beginning, having a treatment gap after, were placed into the mono-pharmacotherapy (discontinue). For example, the patient took TCA from 8/23-9/22, had a gap of 215 days, and then had lidocaine on 4/25. The prescription details follow: 23Aug2006-22Sep2006 (TCA); 25Apr2007-25May2007 (Lido), 06Jun2007-015Jul2007 (TCA); 12Jul2007-11Aug2007 (Lido).



b. Patients who took two agents in the beginning, then had a treatment gap of their two agents after, were placed into the combination pharmacotherapy (discontinue). For example, the patient took pregabalin and gabapentin from 11/13-12/13, and then only pregabalin till 2/2, which means the patient had a treatment gap of pregabalin and gabapentin since 12/13. The prescription details follow: 13Nov2007-13Dec2007 (Gab+ Pre); 26Nov2007- 26Dec2007 (Pre); 03Jan2008-

02Feb2008 (Pre); 15May2008-14Jun2008 (Pre).

Combination Pharmacotherapy (discontinue)



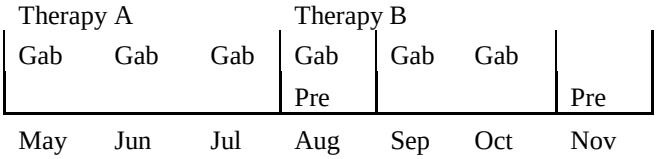
5. Categorize switch and add-on.

   After defining the discontinue group, only the groups of switch and add-on needed to be defined. If patients continued the index prescription until the end of the follow-up, then any second medicines would be counted as a medicine that was add-on. If patients discontinued the index medicine before the end of the follow-up, then the second medicine would be counted as a medicine that was a switch. The definition is aligned with Gore et al., "Therapy switching was defined as a prescription for another medication class within 60 days before or after the date of discontinuation of index therapy. Therapy augmentation was defined as a prescription for another medication class > 60 days before the date of discontinuation or end of follow-up."[113] In other words, the main difference between patients who switch and add on to the treatment is whether they continue the index medicine to the end of the follow-up or not. Following are examples of both groups in mono-and combination pharmacotherapy.

   a. Patients who took one agent in the beginning, started another agent, and discontinued the index medicine to the end of the follow-up were placed into the mono-pharmacotherapy (switch). For example, the

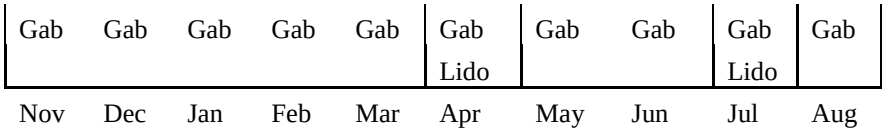
patient started with gabapentin on 5/21, and then switched to pregabalin on 8/16. The prescription details follow: 20May2010-19Jun2010 (Gab); 21Jun2010-21Jul2010 (Gab); 17Jul2010-16Aug2010 (Gab); 16Aug2010-15Sep2010 (Pre+ Gab); 21Sep2010-21Oct2010 (Gab); 29Nov2010-29Dec2010 (Pre).

Mono-pharmacotherapy (switch)



b. Patients who took one agent in the beginning, started another agent, and continued the index medicine to the end of the follow-up, were placed into the mono-pharmacotherapy (add-on). For example, the patient started with gabapentin on 11/16 and then added on lidocaine on 3/30. The prescription details follow: 16Nov2011-16Dec2011 (Gab); 10Dec2011-09Jan2012 (Gab); 10Jan2012-24Feb2012 (Gab); 02Mar2012-01Apr2012 (Gab); 30Mar2012-29Apr2012 (Gab+ Lido); 26May2012-19Jun2012 (Gab); 20Jun2012-20Jul2012 (Gab+ Lido); 21Jul2012-21Aug2012 (Gab).

Mono-pharmacotherapy (add-on)



a. Patients who took two agents in the beginning and discontinued the index medications to the end of the follow-up were placed into the

combination pharmacotherapy (switch). For example, the patient started with pregabalin and TCAs on 11/22, and then switched to pregabalin and duloxetine on 12/3.The prescription details follow: 27Oct2010-21Nov2010 (Pre); 22Nov2010-02Dec2010 (Pre+ TCAs); 03Dec2010-18Jan2011 (Pre+ TCAs+ Dul); 19Jan2011-24Feb2011 (Pre+ Dul); 25Feb2011-22Mar2011 (Dul)

Combination Pharmacotherapy (switch)

Pre TCA	Pre TCA Dul	Pre Dul	Pre Dul	Dul
Nov	Dec	Jan	Feb	Mar

b. Patients who took two agents in the beginning, started a new agent, and continued the index medicine to the end of the follow-up, were placed into the combination pharmacotherapy (add-on). For example, the patient started with pregabalin and gabapentin on 12/11, and then added duloxetine on 6/3. The prescription details follow: 11Dec11-04Mar2008 (Pre+ Gab); 07Mar2008-05Jun2008 (Pre+ Gab); 03Jun2008-02Aug2008 (Dul+ Pre+ Gab).

Combination Pharmacotherapy (add-on)

Pre Gab	Pre Gab	Pre Gab	Pre Gab	Pre Gab	Pre Gab	Pre Gab Dul	Pre Gab Dul	Pre Gab Dul
Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug

c. More examples of the switch group: patients might switch from one medicine to two medications. For example, the patient started with pregabalin on 11/21, and then switched to gabapentin and opioids on

4/21. The prescription details follow: 21Nov2007-21Dec2007 (Pre); 17Dec2007-16Jan2008 (Pre); 23Feb2008-24Mar2008 (Pre); 21Apr2008-21May2008 (Opi+ Gab); 24May2008-23Jun2008 (Opi+ Gab); 21Jun2008-21Jul2008 (Opi+ Gab)

Mono-Pharmacotherapy (Switch)

Pre	Pre	Pre					
				Gab Opi	Gab Opi	Gab Opi	Gab Opi
Dec	Jan	Feb	Mar	Apr	May	Jun	Jul

6. The rest of the patients are in the combination pharmacotherapy nonswitch group.

   For patients who used more than two medications during study period, after defining the groups of discontinue, switch, or add-on, the rest of the patients are placed into combination pharmacotherapy (nonswitch).

   a. Patient started with pregabalin + duloxetine on 5/25/2007 till 4/2/2008. The prescription details follow: 02May2007-18May20007 (Dul); 25May20007-23Aug2007 (Pre+Dul); 27Aug2007-26Sep2007 (Dul); 04Oct2007-02Jan2008 (Pre+Dul); 03Jan2008-02Apr2008 (Pre+ Dul)

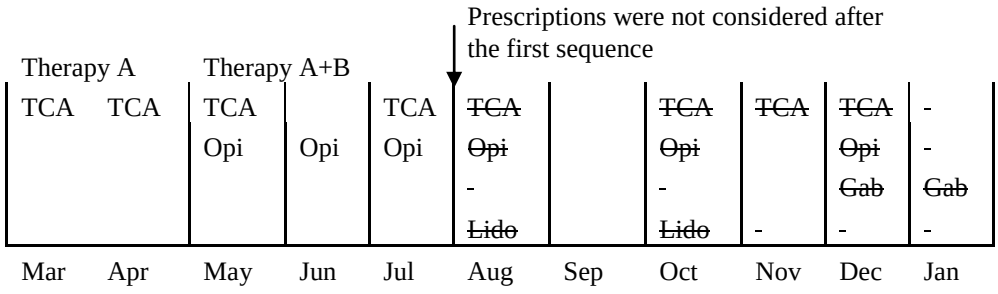
      Combination Pharmacotherapy (nonswitch)

Pre Dul	Pre Dul	Pre Dul	Dul	Pre Dul	Pre Dul	Pre Dul	Pre Dul	Pre Dul	Pre Dul
Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar

7. After the treatment group is categorized, additional changes were not considered.

   For the objectives of this analysis, only the first change of the treatment patterns was considered. Therefore, after the treatment group was categorized,

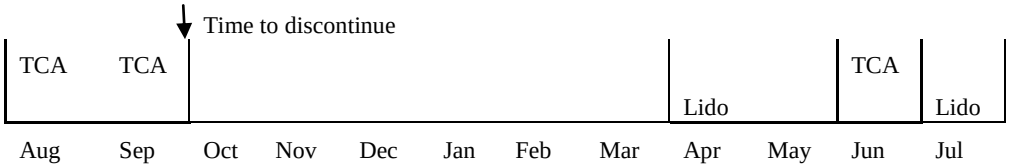
the following sequences were not considered: changing the add-on medicine, switching to another medication after adding-on, for example, the patient started with a TCA on 3/2, and then added on an opioid on 4/18. Even though the patient also added on lidocaine on 8/2, it was not considered in this study. The prescription details follow: 02Mar2010-18Apr2010 (TCAs); 19Apr2010-19May2010 (TCAs+ Opi); 09Jun2010-29Jun2010 (Opi); 30June2010-01Aug2010 (TCAs+ Opi); 02Aug2010-01Sep2010 (TCAs+ Opi+ Lido); 27Sep2010-24Oct2010 (TCAs+ Opi+ Lido); 25Oct2010-25Nov2010 (TCAs); 26Nov2010-10Dec2010 (TCAs+ Opi); 11Dec2010-26Dec2010 (TCAs+ Opi+ Gab); 03Jan2011-02Feb2011 (Gab)



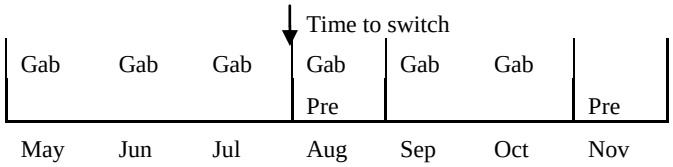
2.3 Outcome Measures

The endpoints of this study were patient distribution in different DPN agents among different treatment groups during the study period. All regimens for the new users with mono-pharmacotherapy and combination pharmacotherapy in DPN patients during 2006 to 2012 were captured and categorized into four groups: discontinue, nonswitch, switch, and add-on. Time to discontinue, time to switch, and time to add on the treatment were calculated in all patients. Time to discontinue was calculated as the number of days

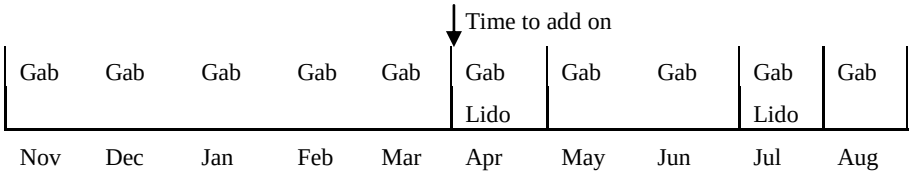
from the index date to the end date of the last prescription prior to discontinuation.



Time to switch was calculated as the number of days from the index date to the first prescription fill date of the switched medicine.



Time to add on was calculated as the number of days from the index date to the first prescription fill date of the add-on medicine.



Other endpoints of this study were the predictors that newly-treated DPN patients would receive combination pharmacotherapy, the odds-ratio of the likelihood to receive combination pharmacotherapy, and the co-morbidities and healthcare costs in both mono- and combination pharmacotherapy groups. The cost data were inflated to 2012 using the US consumer price index for medical care.[114] There were 7 people who had mean costs higher than $1,000,000 during the post-index period. Therefore, the highest 0.25% outliers was replaced as missing; patients who had mean costs higher than $1,001,838 during post-index were replaced as missing.

2.4 Independent Variables

The dependent variables represent the outputs or effects, and the independent variables represent the inputs or causes. The dependent variables of this study were defined as whether the patients were using combination pharmacotherapy on the index date or not. And the independent variables of this study were age, gender, region, and the insurance plan, which were determined on the index date. Insurance plan was classified as: Commercial, Medicaid (Children's Health Insurance program (CHIP), Medicaid disabled, Medicaid low income, Medicaid restrict), Medicare (Special needs plan-chronic condition, Special needs plan-dual eligible, Special needs plan-institutionalized, Medicare cost, Medicare risk), and Self-Insured.

Regions included all 50 states and the District of Columbia and Puerto Rico, and were classified as the following: West (Arizona, Colorado, Idaho, New Mexico, Montana, Utah, Nevada, Wyoming, Alaska, California, Hawaii, Oregon, Washington), Midwest (Indiana, Illinois, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota), Northeast (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, Pennsylvania), South (Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, Texas), and Puerto Rico.[115]

Co-morbidities are another independent variable and described in both pre- and post-index periods.[93] The pre-index co-morbidities were identified in pre-index period, and post-index co-morbidities were identified in post-index period. The pre-index period was 6 months prior to the index date, which was the first DPN prescription filled date,

and the follow-up period was 1 year after the index date. The ICD-9 code of each co-morbidity is displayed in Table 2.3.

2.5 Data Analysis

2.5.1 Descriptive Statistics

Stata SE v. 13 (StataCorp, College Station, Tx) and SAS 9.3 were used for statistical analysis. Descriptive statistics were used to describe DPN treatment patterns and distributed into the discontinue group, the nonswitch group, the switch group, or the add-on group. The healthcare costs were reported in mean, median, interquartile range (IQR) for each group, and the costs were used to compare between patients with and without combination pharmacotherapy.

Numbers of co-morbidities were categorized into three groups: patients who had one to four co-morbidities, five to seven co-morbidities, and above seven co-morbidities. These groups were selected since the median of co-morbidities were five in pre-index, and the median of co-morbidities were seven in post-index. The co-morbidities were also categorized into different disease groups. If patients had myocardial infraction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, coronary heart disease, hypertension, or hyperlipidemia, then they would be classified as having a cardiovascular disorder. If patients had retinopathy, or nephropathy, then they would be classified as having a diabetes-related condition. If patients had depression, bipolar disorder, or anxiety, then they would be classified as having a mental disorder. If patients had insomnia, then they would be classified as having as a sleep disorder. If patients had arthritis and other arthropathies, rheumatoid arthritis, low back pain, back and neck pain,

Table 2.3 ICD-9 Codes of the Co-morbidities

Disease	ICD-9 Codes
Cardiovascular disorders	
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-9, 428.x
Peripheral vascular disease	093.0, 437.3, 440.x, 441.x, 443.1-443.9, 447.1, 557.1, 557.9, v43.4
Cerebrovascular disease	362.34, 430.x-438.x
Coronary heart disease	410.xx-414.xx
Hypertension	401.x
Hyperlipidemia	272.0, 272.1, 272.2, 272.4
Diabetes-related conditions	
Retinopathy	362.01, 362.02
Nephropathy	582.xx, 583.0-4, 583.6, 583.7, 585, 586, 588.0, 588.1, 588.8, 588.9
Chronic renal failure	585.xx
Mental disorders	
Depression	296.2x, 296.3x, 300.4, 311
Bipolar disorder	296.4x, 296.5x, 296.6x, 296.7
Anxiety	300.00, 300.5, 300.09, 300.20, 300.20, 300.22, 300.23, 300.29, 300.3, 308.3
Sleep disorders	
Insomnia/sleep disorders	780.5x, 307.4x, 347.0x, 347.1x, v69.4
Musculoskeletal pain conditions	
Arthritis and other arthropathies	711.xx, 712.xx, 713.x, 714.4x, 714.8x, 714.9x, 716.xx, 717.xx, 718.xx, 719.xx
Rheumatoid arthritis	714.0, 714.1, 714.2
Low back pain	720.1x, 721.3x, 721.9x, 722.1x, 724.02, 724.2x, 724.5x, 724.8x, 733.02
Back and neck pain, other than low back pain	720.81, 720.89, 720.9, 721.0, 721.2, 721.5-721.9, 722.11, 722.30, 722.31, 722.39, 722.4, 722.6, 722.80-722.82, 722.90-722.92, 723.x (except 723.4), 724.01, 724.1, 724.8, 724.9, 737.10-737.12, 737.19-737.22, 737.29, 737.30, 756.10, 756.13-756.17, 756.19, 805.8, 847.9
Rheumatism, excluding the back	725 to 728.9, 729.3-729.9

or rheumatism, then they would be classified as having a musculoskeletal pain condition.

2.5.2 Bivariate Analyses of Demographics

Distribution of age, gender, region, insurance type, and the number of co-morbidities were compared between patients with and without combination pharmacotherapy. Gender, region, insurance type, and the co-morbidities are categorical variables and were normally distributed in this study, so the Pearson's chi-square test was used. Age was a continuous variable and was normally distributed in this study, so the Student t-test was used. The pre-index and post-index enrollment days were continuous variables and were nonparametric distributed in this study, so the Wilcoxon Mann-Whitney test was used.

The proportions of the treatment groups were not normally distributed and were being compared among six index medications, so the Kruskal Wallis test was used. The healthcare costs were not normally distributed and were being compared between patients with and without combination pharmacotherapy, so the Wilcoxon Mann-Whitney test was used.

2.5.3 Kaplan-Meier Analysis

The continuation of mono- and combination pharmacotherapy is being calculated through Kaplan-Meier survival function. The time to switch or add on to another medication in either mono- or combination pharmacotherapy was also calculated through Kaplan-Meier survival function.

For example, for calculation of the time to discontinue in patients with

combination pharmacotherapy, each patient was followed until either the time that the combination pharmacotherapy was discontinued or the end of the follow-up. The cumulative survival function $\hat{S}[t]$ is the proportion of subjects who continued the combination pharmacotherapy at time t. The probability that a patient continued the mono-pharmacotherapy the first t days is the joint probability of continuing days. This probability was estimated by $\hat{S}(t)=p_1p_2p_3\ldots p_t$. If there were no discontinuation, the probability (p) would equal one on all days, and this estimate is called the Kaplan-Meier survival function.

The Kaplan-Meier survival function was calculated for the combination pharmacotherapy, where p_{k1} is the probability of continuing the combination pharmacotherapy on the k^{th} day on which discontinuation occurred, and the equation is below:

$$\hat{S}(t) = \prod_{\{k:t_{k1}<t\}} p_{k1}$$

The p_{k2} is the probability of continuing the mono-pharmacotherapy on the k^{th} day on which discontinuation occurred, and the equation is below:

$$\hat{S}(t) = \prod_{\{k:t_{k2}<t\}} p_{k2}$$

The Kaplan-Meier survival function was not only determined for the treatment discontinuation, but also the time to switch or add on another medication in both mono- and combination pharmacotherapy. The same treatment patterns were also determined in the six index medicines in the mono-pharmacotherapy group.

2.5.4 Simple Proportional Hazards Model

The hazard function λ[t] is the instantaneous rate per unit time at which people were discontinued at time t. λ[t] = 0 implies that there was no risk of discontinuation. Large values of λ[t] implies a rapid rate of decline in S[t].

$$\lambda(t) = \frac{\Pr\left[patient\ discontinue\ by\ time\ t\right] + \Delta t[patient\ continue\ the\ Rx\ at\ time\ t]}{\Delta t}$$

Hazard ratio (R) is the risk (discontinuation) of combination pharmacotherapy at time t relative to mono-pharmacotherapy. The equation for the hazard ratio of the combination pharmacotherapy discontinuation is as follows:

$$\frac{\lambda_{\text{combination pharmacotherapy}}[\text{t}]}{\lambda_{\text{mono-pharmacotherapy}}[\text{t}]} = \frac{\text{R}\,\lambda_{\text{mono-pharmacotherapy}}[\text{t}]}{\lambda_{\text{mono-pharmacotherapy}}[\text{t}]} = R$$

Simple hazard regression model was used to calculate the relative risk of discontinuation, switch, and add-on associated with patients who used combination pharmacotherapy. The reference group was mono-pharmacotherapy, and e^{β} is the relative risk (discontinuation) of combination pharmacotherapy relative to mono-pharmacotherapy, and the equation is below:

$$\lambda_{\text{combination pharmacotherapy}}[t]e^{\beta}\,[t] \;\; / \lambda_{\text{mono-pharmacotherapy}}\,[t] \;= e^{\beta}$$

A 95% confidence interval for this relative risk was Ŕexp[±1.96 x se [β]]. If two treatments were equally effective, the relative risk would be one, and β would be zero. Below is the regression model for the risk of discontinuation in combination pharmacotherapy:

$$\lambda_{\text{combination pharmacotherapy}}\,[t]= \lambda_{\text{mono-pharmacotherapy}}\,[t]\,\exp[\beta\,(\text{group}x_i)]$$

For mono-pharmacotherapy patients, TCAs was the reference medicine, since it is proven to be effective and inexpensive. The hazard ratio of opioids discontinuations compared to TCAs was calculated, and the equation is below:

$$\frac{\lambda_{\text{opioids}}[t]}{\lambda_{\text{TCAs}}[t]} = \frac{\text{R}\,\lambda_{\text{TCAs}}[t]}{\lambda_{\text{TCAs}}[t]} = R$$

The following hazard ratio were also calculated: duloxetine vs. TCAs, gabapentin vs. TCAs, pregabalin vs. TCAs, and lidocaine vs. TCA. Simple hazard regression model was not only used to calculate the relative risk of discontinuation, switch, and add-on associated with patients who used combination pharmacotherapy, but was also used to calculate the relative risk of the patterns associated with patients who used opioids, duloxetine, gabapentin, pregabalin, or any route lidocaine, and the reference group were the patients who used TCAs.

2.5.5 Multiple Logistic Regression

For each model, the dependent variable was a dichotomous indicator coded as "1" for patients in the combination cohort, and "0" for patients with mono-pharmacotherapy. Age, gender, insurance plan type, region, and the numbers of co-morbidities were covariates that measured on the i^{th} patient. Table 2.4 is one of the odds ratio tables in this study. The covariate in Table 2.3 is co-morbidities, and the patients can be grouped into with or without co-morbidities.

The odds ratio is measured by the Mantel-Haenszel estimate, and it means the odds of the patients to use combination pharmacotherapy in the certain co-morbidity.

Table 2.4 Odds Ratio Table

	Co-morbidity (yes)	Co-morbidity (no)	Total
Combination pharmacotherapy	d_{1j}	d_{0j}	m_{1j}
Mono-Pharmacotherapy	c_{1j}	c_{0j}	m_{0j}
Total	n_{1j}	n_{0j}	N_j

$$W_j = \frac{d_{1j}c_{0j}}{N_j}$$

$$W = \sum w_j$$

$$\Psi_{mh} = \sum \frac{d_{1j}c_{0j}/N_j}{W}$$

The first model in our study was to test the relationship between age, sex, insurance type, region, the numbers of co-morbidities and the chance to be in combination pharmacotherapy in all patients. The proposed equation was:

$$\text{logit}[E[d_i| x_i]] = \alpha + \beta_1 [\text{age categories}] + \beta_2[\text{insurance type}] + \beta_3[\text{sex}] + \beta_4[\text{regions}] + \beta_5 [\text{co-morbidities categories}]$$

The second model was to test the relationship between each co-morbidity and the chance to be in combination pharmacotherapy in all patients. The proposed equation is:

$$\text{logit}[E[d_i| x_i]] = \alpha + \beta_1 [\text{myocardial infraction}] + \beta_2[\text{congestive heart failure}] + \beta_3[\text{peripheral vascular disease}] + \beta_4[\text{cerebrovscular disease}] + \beta_5 [\text{coronary heart disease}] + \beta_6 [\text{hypertension}] + \beta_7[\text{hyperlipidemia}] + \beta_8[\text{retinopathy}] + \beta_9[\text{nephropathy}] + \beta_{10}$$

[depression] + β_{11}[bipolar disorder] + β_{12} [anxiety] + β_{13} [insomnia] + β_{14} [arthritis and other arthropathies]+ β_{15} [rheumatoid arthritis] + β_{16} [low back pain] + β_{17} [back and next pain] + β_{18} [rheumatism]

The third model was to test the relationship between cardiovascular disorders, diabetes-related condition, mental disorders, sleep disorders, musculoskeletal pain conditions and the chance to be in combination pharmacotherapy in all patients.
The proposed equation was:

$$\text{logit}[E[d_i| x_i]]= \alpha+ \beta_1 [\text{Cardiovascular disorders}] + \beta_2[\text{Diabetes-related condition}]+ \beta_3[\text{Mental disorders}] + \beta_4[\text{Sleep disorders}] + \beta_5 [\text{Musculoskeletal pain conditions}]$$

To interpret the result, exp [β_1] was the combination pharmacotherapy odds ratio in myocardial infraction compared with mono-pharmacotherapy adjusted for other co-morbidities. If the model covariates had no effect on the response variable, then all of the β parameters associated with the covariates would equal zero. The probability of d_i=1 given the covariates x_i was denoted $o[x_{i1,} x_{i2},\ldots, x_{iq}]=o[x_i]$ and equals $E[d_i| x_i]$

Then the multiple logistic regression model assumed that d_i has a Bernoulli distribution. Not like single logistic regression model, the multiple logistic model includes more than one covariate. Pearson chi-square goodness-of-fit test was used to determine whether the model gives a good fit to data. Because all the covariates in the model were categorical variables, Pearson chi-square goodness-of-fit test is the most

suitable approach. Hosmer-Lemeshow test is recommended to use if the covariates have continuous variable.[116]

The residual for the j^{th} covariate pattern is $d_j - n_j \hat{o}_j$. Substituting $\hat{o}_j$ for o_j in the Equation gives the Pearson residual, which is

$$r_j = \frac{d_j - n_j \hat{o}_j}{\sqrt{n_j \hat{o}_j (1 - \hat{o}_j)}}$$

If model is correct and n_j is sufficiently large, then the equation below will have a chi-squared distribution with *J*- (q+1) degrees of freedom. The equation is the Pearson chi-squared goodness-of-fit statistic. It can be used as a goodness-of-fit test of model as long as *J*, the number of distinct covariate patterns, is small in comparison with the number of study subjects. A conservative rule of thumb is that the estimated expected number of events $n_j \hat{o}_j$ should be at least 5 and not greater than $n_j - 5$ for each distinct pattern of covariates. In this case we can reject model if the p-value associated with the chi-square is less than 0.05.

$$x^2 = \sum r_j^2$$

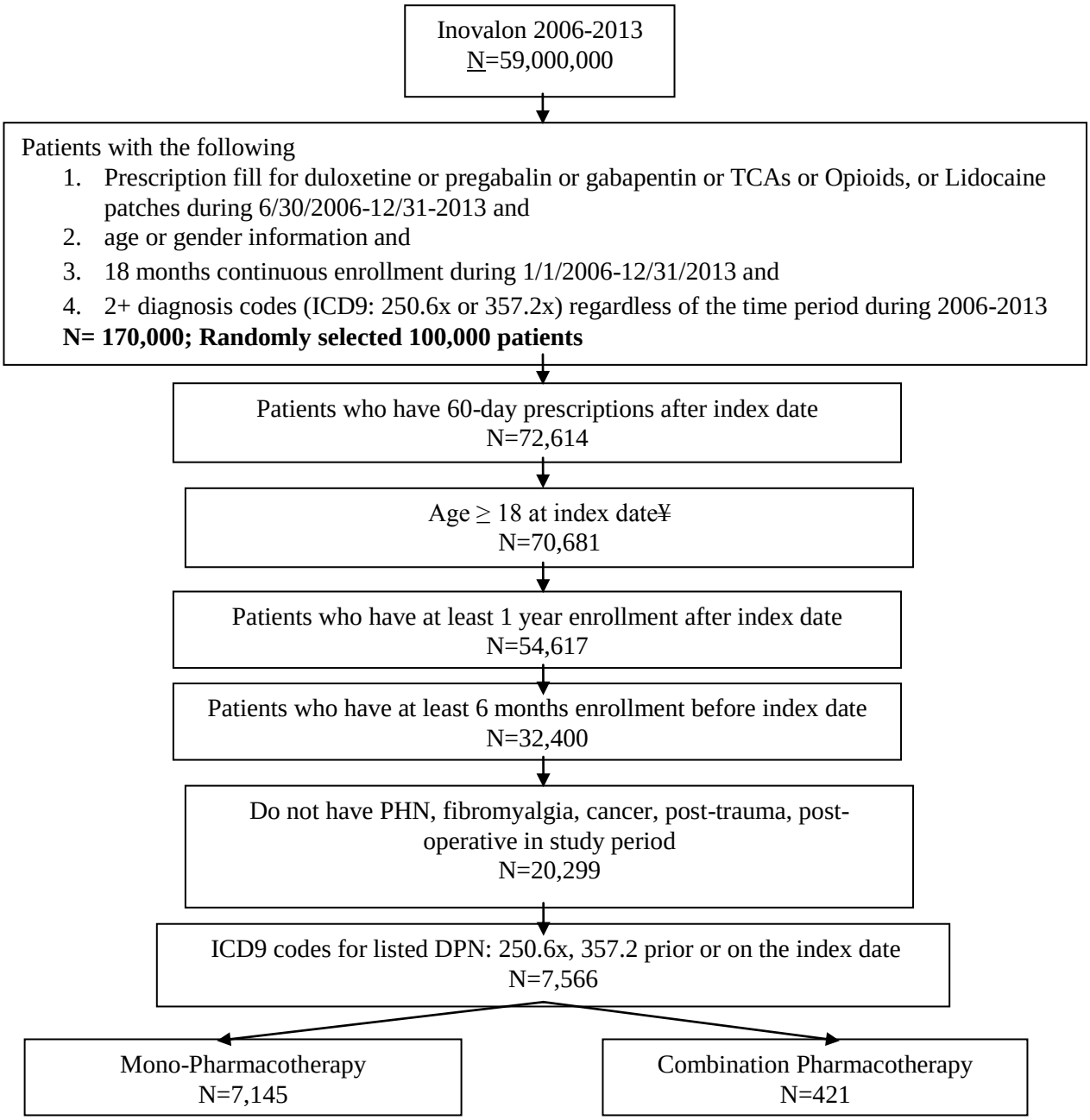
CHAPTER 3

RESULTS

3.1 Study Cohort

There were approximately 59 million patients in the Inovalon database during 2006-2013. The first screening was done by Inovalon, with inclusion criteria consisting of at least 2 diagnosis codes of DPN (ICD9 code: 250.6x or 357.2x), having 18 months continuous enrollment, age and gender information, and with prescriptions for one or more of the following: TCAs, opioids, duloxetine, gabapentin, pregabalin, or lidocaine. Approximately 170,000 patients met the above criteria, which exceeded the amount of data Inovalon would provide for a thesis project; therefore, 100,000 patients were randomly selected. The randomization process was by a computer through choosing among the100,000 ID numbers that were assigned by Inovalon.

The distribution of the patients is presented in Figure 3.1. Of the 100,000 baseline patients, 72,614 of them have at least one 60-day or longer prescription for DPN after the index date, and there are 32,400 patients with 6-month pre-index and one-year post-index enrollments. Out of these, 7,566 patients have a DPN diagnosis code without PHN, fibromyalgia, cancer, post trauma, or post operative disease. Among them, 7,145 patients use mono-pharmacotherapy, which means they use one medicine on the index date, and 421 patients use combination pharmacotherapy, which means they use two or more



¥ Index date: the first prescription fill for DPN drug during the identification period

Figure 3.1 Patient with DPN in Inovalon from 1.1, 2006 – 12. 31, 2013

medicines within 30 days from the index date.

3.1.1 Availability of HbA1c, Provider, and Costs in this Study Cohort

The provider information and HbA1c value were also captured in this study; however, due to the proportions of missing data on these two variables, they were not used for the analysis. Table 3.1 and Table 3.2 are the details of these two variables. Due to the limited data for patients with costs, the characteristics of the patients with available cost data were examined. Table 3.3 shows 2,361 patients with mono-pharmacotherapy (36.8%) and 150 patients with combination pharmacotherapy have cost information (39.4%). Patients who are self-insured have zero missing in cost data, and patients who have commercial insurance have more missing (68.8%) than Medicaid

Table 3.1 HbA1c Value in Pre-Index

	N	Mean± SD (HbA1c)	Median (HbAlc)	Good Control (HbA1c ≤7)	Poor Control (HbA1c >7)
Mono-pharmacotherapy	2066 (28.9%)	7.65± 1.76	7.15	963 (46.6%)	1103 (53.3%)
Combination pharmacotherapy	92 (21.9%)	7.60± 1.96	7.05	46 (50%)	46 (50%)

Table 3.2 Provider Information of the Cohort

	Pain-related specialties[†]	Primary Care[‡]	Other specialty	Missing	Total
Mono-pharmacotherapy	45 (0.6%)	329 (4.6%)	201 (2.8%)	6270 (87.8%)	7145
Combination pharmacotherapy	3 (0.7%)	45 (10.7%)	10 (2.4%)	363 (86.2%)	421

[†] Neurological surgery, Psychiatry & Neurology

[‡] Family medicine, hospitalist, internal medicine, nurse practitioner, obstetrics & gynecology, pediatrics

Table 3.3 Availability of Costs by Patient Characteristics

	Missing		≤$400		$400<X<$500,000		>$500,000		Total
Mono-pharmacotherapy	4517	63.22%	344	4.81%	2276	31.85%	6	0.08%	7145
Combination pharmacotherapy	255	60.57%	10	2.38%	158	37.53%	0	0.00%	421
18-44	278	63.33%	15	3.42%	146	33.26%	0	0.00%	439
45-64	2069	63.02%	142	4.33%	1068	32.53%	4	0.12%	3283
≥65	2425	63.09%	197	5.12%	1220	31.74%	2	0.05%	3844
Male	2187	63.78%	170	4.96%	1069	31.18%	3	0.09%	3429
Female	2585	62.48%	184	4.45%	1365	32.99%	3	0.07%	4137
Commercial	1152	68.82%	78	4.66%	444	26.52%	0	0.00%	1674
Medicaid	512	44.48%	40	3.48%	598	51.95%	1	0.09%	1151
Medicare	2588	61.93%	228	5.46%	1358	32.50%	5	0.12%	4179
Self-Insured	0	0.00%	1	8.33%	11	91.67%	0	0.00%	12
Missing	520	94.55%	7	1.27%	23	4.18%	0	0.00%	550
West	801	72.49%	76	6.88%	228	20.63%	0	0.00%	1105
Midwest	1026	79.91%	33	2.57%	225	17.52%	0	0.00%	1284
Northeast	735	46.49%	80	5.06%	765	48.39%	1	0.06%	1581
South	1881	63.59%	143	4.83%	929	31.41%	5	0.17%	2958
Puerto Rico	134	31.60%	21	4.95%	269	63.44%	0	0.00%	424
Missing	195	91.12%	1	0.47%	18	8.41%	0	0.00%	214
With 1-4 comorbidities	755	64.75%	103	8.83%	308	26.42%	0	0.00%	1166
With 5-7 comorbidities	2143	63.22%	167	4.93%	1078	31.80%	2	0.06%	3390
With >7 comorbidities	1874	62.26%	84	2.79%	1048	34.82%	4	0.13%	3010
2006	1029	87.87%	44	3.76%	98	8.37%	0	0.00%	1171
2007	1226	71.82%	55	3.22%	426	24.96%	0	0.00%	1707
2008	542	47.29%	76	6.63%	528	46.07%	0	0.00%	1146
2009	825	69.39%	34	2.86%	329	27.67%	1	0.08%	1189
2010	602	64.04%	41	4.36%	295	31.38%	2	0.21%	940
2011	378	45.76%	62	7.51%	384	46.49%	2	0.24%	826
2012	170	28.96%	42	7.16%	374	63.71%	1	0.17%	587

(44.5%) and Medicare (61.9%). Patients who live in Puerto Rico have less missing (31.6%) in cost data, and patients who live in the Midwest have more missing (79.9%) than those living in the West (72.5%), South (63.6%), and Northeast (46.5%). Year 2006 has a lot more missing data (87.9%) compared to year 2012 (29.0%).

3.1.2 Demographic Characteristics of DPN Patients

There were 7,145 patients with mono-pharmacotherapy and 421 patients with combination pharmacotherapy. Patients in the mono-pharmacotherapy group were older than patients in combination pharmacotherapy group by around four years (64.6± 11.7 vs. 60.6±11.5 $p<0.001$). Both the mono- and combination pharmacotherapy group had more females than males, but it was not statistically significantly different ($p=0.111$). More mono-pharmacotherapy patients used Medicare insurance compared to combination pharmacotherapy patients (56% vs. 46%), but fewer mono-pharmacotherapy patients used Medicaid (15% vs. 19%), and commercial insurance (22% vs. 27%) compared to combination pharmacotherapy patients. Overall, there was a statistically significant difference in insurance between mono- and combination pharmacotherapy group ($p=0.001$). More mono-pharmacotherapy patients lived in the West (15% vs. 12%) and Puerto Rico (6% vs. 3%), fewer of them lived in Midwest (17% vs. 20%) and Northeast (21% vs. 25%) compared with combination pharmacotherapy patients, and it was statistically significantly different ($p=0.007$). Fewer mono-pharmacotherapy patients had over seven co-morbidities compared with combination pharmacotherapy patients (19% vs. 24%), and it was a statistically significantly different ($p=0.038$). In terms of the enrollment days, mono-pharmacotherapy patients had longer pre-index enrollment days

(625 vs.578) and shorter post-index enrollment days (819 vs. 836) than combination pharmacotherapy patients, but differences were not statistically significantly (pre-index: p=0.342; post-index p=0.404) (Table 3.4).

3.1.3 Co-morbidities of DPN Patients

3.1.3.1 Results Against Hypothesis 2: People Who Take Combination Pharmacotherapy Have More Co-morbidities than Patients Who Take Mono-pharmacotherapy

Table 3.5 shows the clinical co-morbidities of DPN patients in 6-month pre-index, and Table 3.6 shows the co-morbidities in 1-year post-index. In both pre- and post-index, the most common co-morbidity for the DPN patients is cardiovascular disorders (pre-index: 89.3%; post-index: 95.8%), and the second-most common one is musculoskeletal pain conditions (pre-index: 59.4%; post-index: 74.5%), diabetes-related conditions (pre-index: 24.4%; post-index: 35.5%), mental disorders (pre-index: 17.1%; post-index: 24.3%), sleep disorders (pre-index: 8.9%; post-index:14.6%). Overall, patients have higher percentage in each co-morbidity in post-index compared with pre-index, indicating patients have more co-morbidities after taking DPN medications.

To compare patients with mono-pharmacotherapy and combination pharmacotherapy, there were fewer patients with mental disorders (pre-index: 17% vs. 24%, $p<0.001$; post-index: 24% vs. 36%, $p<0.001$) and musculoskeletal pain conditions (pre-index: 59% vs. 66%, $p=0.003$; post-index: 74% vs. 86%, $p<0.001$) in mono-pharmacotherapy group during study period. However, there were no statistically significantly differences in patients with cardiovascular disorders (pre-index: 0.070; post-index: 0.169), and diabetes-related condition (pre-index: 0.259; post-index: 0.378) during

Table 3.4 Demographic Characteristics of Diabetic Painful Neuropathy Patients

	Mono-pharmacotherapy (n=7145)		Combination pharmacotherapy (n=421)		P Value
Age(y), mean (standard deviation)	64.6±11.7		60.6±11.5		<0.001
18-44	400	6%	39	9%	<0.001
45-65	3056	43%	227	54%	
>=65	3689	52%	155	37%	
Gender					0.111
Male	3254	46%	175	42%	
Female	3891	54%	246	58%	
Insurance Plan Type					0.001
Commercial	1559	22%	115	27%	
Medicaid	1069	15%	82	19%	
Medicare	3985	56%	194	46%	
Missing	522	7%	30	7%	
Region					0.007
West	1056	15%	49	12%	
Midwest	1199	17%	85	20%	
Northeast	1477	21%	104	25%	
South	2795	39%	163	39%	
Puerto Rico	412	6%	12	3%	
Missing	206	3%	8	2%	
Numbers of Comorbidities					
With1-4 comorbidities	2343	33%	137	33%	0.038
With5-7 comorbidities	3465	48%	185	44%	
With >7 comorbidities	1337	19%	99	24%	
Pre-index enrollment days (Median)	625		578		0.342
Post-index enrollment days (Median)	819		836		0.404

Table 3.5 Clinical Co-morbidities of Diabetic Painful Neuropathy Patients (pre-index: 6 months)

	Mono-pharmacotherapy		Combination pharmacotherapy		P Value
	(n=7145)		(n=421)		
Cardiovascular disorders	6395	90%	365	87%	0.070
Congestive heart failure	1010	14%	64	15%	0.542
Peripheral vascular disease	1622	23%	96	23%	0.961
Cerebrovascular disease	817	11%	47	11%	0.865
Coronary heart disease	1830	26%	105	25%	0.759
Hypertension	5326	75%	296	70%	0.053
Hyperlipidemia	4748	66%	264	63%	0.114
Diabetes-related conditions	1752	25%	93	22%	0.259
Retinopathy	848	12%	42	10%	0.242
Nephropathy	1191	17%	64	15%	0.432
Mental disorders	1191	17%	101	24%	<0.001
Depression	972	14%	87	21%	<0.001
Bipolar disorder	68	1%	6	1%	0.337
Anxiety	345	5%	25	6%	0.305
Sleep disorders	633	9%	38	9%	0.907
Insomnia/sleep disorders	633	9%	38	9%	0.907
Musculoskeletal pain conditions	4217	59%	279	66%	0.003
Arthritis and other arthropathies	2061	29%	165	39%	<0.001
Rheumatoid arthritis	153	2%	9	2%	0.996
Low back pain	1570	22%	126	30%	<0.001
Back and neck pain, other than low back pain	774	11%	57	14%	0.084
Rheumatism, excluding the back	2543	36%	158	38%	0.420

Table 3.6 Clinical Co-morbidities of Diabetic Painful Neuropathy Patients (post-index: 1 year)

	Mono-pharmacotherapy		Combination pharmacotherapy		P Value
	(n=7145)		(n=421)		
Cardiovascular disorders	6853	96%	398	95%	0.169
Congestive heart failure	1478	21%	88	21%	0.915
Peripheral vascular disease	2329	33%	139	33%	0.858
Cerebrovascular disease	1338	19%	83	20%	0.614
Coronary heart disease	2507	35%	151	36%	0.745
Hypertension	6134	86%	356	85%	0.462
Hyperlipidemia	5706	80%	330	78%	0.464
Diabetes-related conditions	2544	36%	141	33%	0.378
Retinopathy	1319	18%	80	19%	0.781
Nephropathy	1775	25%	97	23%	0.405
Mental disorders	1684	24%	151	36%	<0.001
Depression	1390	19%	128	30%	<0.001
Bipolar disorder	81	1%	8	2%	0.156
Anxiety	565	8%	45	11%	0.042
Sleep disorders	1021	14%	87	21%	<0.001
Insomnia/sleep disorders	1021	14%	87	21%	<0.001
Musculoskeletal pain conditions	5270	74%	364	86%	<0.001
Arthritis and other arthropathies	3125	44%	233	55%	<0.001
Rheumatoid arthritis	248	3%	13	3%	0.676
Low back pain	2296	32%	187	44%	<0.001
Back and neck pain, other than low back pain	1295	18%	112	27%	<0.001
Rheumatism, excluding the back	3474	49%	241	57%	0.001

the study period. For sleep disorders, fewer patients in the mono-pharmacotherapy group had the disease in post-index (14% vs. 21%, p<0.001), but there was not a statistically significantly difference in pre-index (p=0.907) (Table 3.5, Table 3.6).

Among specific co-morbidity, most differences are not statistically significantly different between patients with mono- and combination pharmacotherapy. However, there were fewer patients with depression (pre-index: 14% vs. 21%, p<0.001; post-index: 24% vs. 36%, p<0.001), arthritis and other arthropathies (pre-index: 29% vs. 39%, p=0.003; post-index: 44% vs. 55%, p<0.001), and low back pain (pre-index: 22% vs. 30%, p=0.003; post-index: 32% vs. 44%, p<0.001) in mono-pharmacotherapy group during study period. For back/ neck pain and rheumatism, fewer patients in the mono-pharmacotherapy group had the disease in post-index, but there was no statistically significantly different in pre-index. Overall, patients with combination pharmacotherapy had more co-morbidities than patients with mono-pharmacotherapy (Table 3.5, 3.6).

3.2 Treatment Patterns of DPN Patients

3.2.1 Results Against Hypothesis 1: Patients Who Take Combination Pharmacotherapy Are Less Likely to Discontinue, Switch, or Add on Another Treatment than Patients Who Take Mono-pharmacotherapy

Figure 3.2 shows that from 2006 to 2012, the percentages of the patients who use mono-pharmacotherapy and the patients who use combination pharmacotherapy have not changed. There are around 94% to 96% of the patients with mono-pharmacotherapy, and around 4% to 6% of the patients with combination pharmacotherapy. Table 3.7 shows the patient distribution in different DPN agents among different treatment groups during the study period. Most patients use one agent (n=6,261, 82.8%), but some patients use more

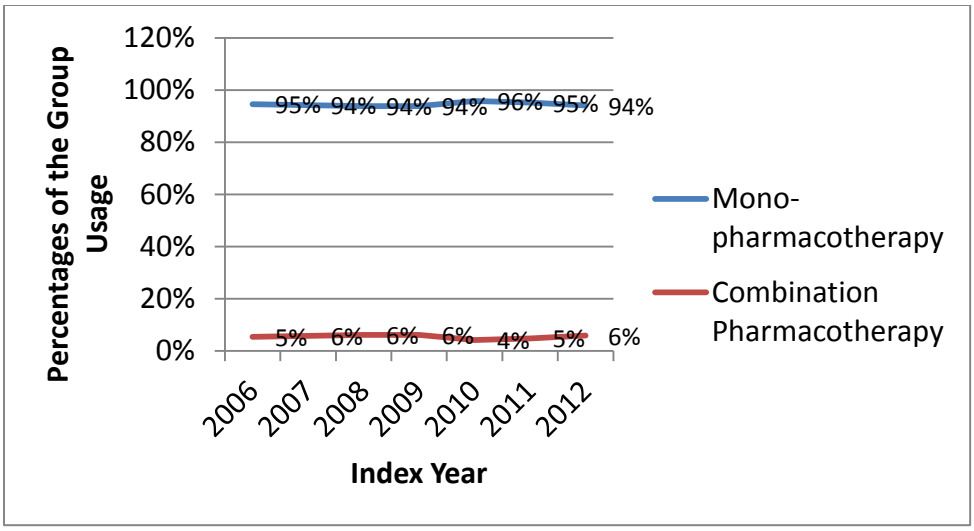


Figure 3.2 Percentages of Mono- and Combination Pharmacotherapy from 2006-2012

than one agent, which means a single agent did not effectively treat those patients. There are 1,128 patients who use two agents, 165 patients who use three agents, 11 patients who use four agents, and one patient who uses five agents. Overall, it is more common for patients to use one agent through the study period. Among patients who use mono-pharmacotherapy, 2,420 of them are in the discontinued group (33.9%), 4,162 of them are in the nonswitch group (58.3%), 260 of them are in the switch group (3.6%), and 303 of them are in the add-on group (4.2%). Among patients who use combination pharmacotherapy, 199 of them are in the discontinued group (47.3%), 170 of them are in the nonswitch group (40.4%), 23 of them are in the switch group (5.5%), and 29 of them are in the add-on group (6.8%). Overall, combination pharmacotherapy patients have a lower proportion of nonswitch than mono-pharmacotherapy patients (40% vs. 58%), but having a higher percentage in discontinuation (47% vs. 34%), switch (5% vs. 4%) and add-on (7% vs. 4%).

Table 3.7 Patient Distribution in Different DPN Agents Among Different Treatment Groups During the Study Period

Treatment Groups	Number of Drugs used During Study Period											
	One		Two		Three		Four		Five		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Mono-Pharmacotherapy												
Discontinue	2099	34%	301	37%	20	27%	0	0%	0	0%	2420	34%
Non-Switch	4162	66%	0	0%	0	0%	0	0%	0	0%	4162	58%
Switch	0	0%	230	29%	30	41%	0	0%	0	0%	260	4%
Add-on	0	0%	272	34%	25	33%	6	100%	0	0%	303	4%
Total	6261	100%	803	100%	75	100%	6	100%	0	100%	7145	100%
Combination Pharmacotherapy												
Discontinue	0	0%	163	50%	35	38%	1	20%	0	0%	199	47%
Non-Switch	0	0%	161	50%	9	10%	0	0%	0	0%	170	40%
Switch	0	0%	0	0%	30	33%	2	40%	1	100%	23	5%
Add-on	0	0%	0	0%	27	30%	2	40%	0	0%	29	7%
Total	0	0%	324	100%	91	100%	5	100%	1	100%	421	100%

Table 3.8 shows that patients who take mono-pharmacotherapy discontinue in a mean of 74.4 days, which is shorter than the time of the patients who take combination pharmacotherapy (111.9 days), and patients who take combination pharmacotherapy are 1.30 times as likely to discontinue as patients who take mono-pharmacotherapy (95% CI: 1.31- 1.51, $p<0.001$) (Figure 3.3). Patients who take combination pharmacotherapy switch to another medication in a mean of 124.3 days, which is shorter than the patients who take mono-pharmacotherapy (143.4 days). However, there is no statistically significantly different between mono- and combination pharmacotherapy patients in time to add on ($p=0.254$) (Figure 3.4). Patients who take mono-pharmacotherapy add on another medication in a mean of 125.5 days, which is shorter than the patients who take combination pharmacotherapy (133.5 days). However, there is no statistically

Table 3.8 Switching, Add-on, and Discontinuation of Therapy of Different Groups

	Mono-pharmacotherapy	Combination Pharmacotherapy
Discontinue (N)	2420 (33.9 %)	199 (47.3 %)
Days to discontinuation, mean	74.4	114.4
Median	49	98
Hazard Ratio	Ref	1.30
95% Confidence Interval	Ref	1.13- 1.51
P value	Ref	< 0.001
Switch (N)	260 (3.6 %)	23 (5.5 %)
Days to switching, mean	143.4	124.3
Median	127.5	103
Hazard Ratio	Ref	1.28
95% Confidence Interval	Ref	0.84- 1.96
P value	Ref	0.254
Add-on (N)	303 (4.2 %)	29 (6.9 %)
Days to augmentation, mean	125.3	133.5
Median	99	100
Hazard Ratio	Ref	1.42
95% Confidence Interval	Ref	0.97-2.09
P value	Ref	0.069

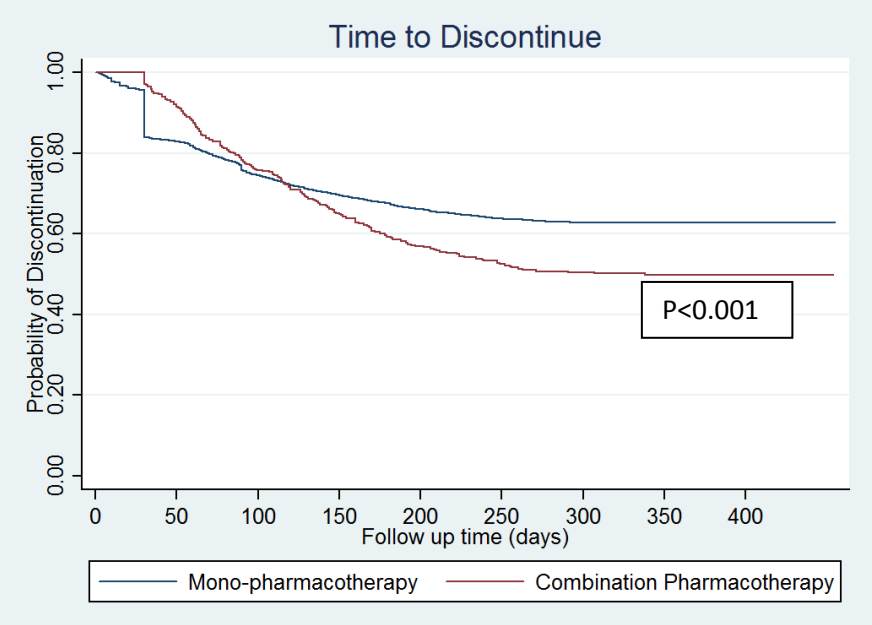


Figure 3.3 Kaplan-Meier Curve of Time to Discontinue Among Different Groups

significantly difference between mono- and combination pharmacotherapy patients in time to add on (p=0.069) (Figure 3.5).

3.2.2 Treatment Patterns in Mono-pharmacotherapy Group

Most mono-pharmacotherapy patients started with gabapentin (n=3980, 55.7%), followed by opioids (n=936, 13.1%), pregabalin (n=920, 12.9%), TCAs (n=817, 11.4%), duloxetine (n=385, 5.4%), and lidocaine (n=107, 1.5%) for their index medicine. Patients who started with an opioid had the highest percentage to discontinue (51%), followed by patients who started with lidocaine (49%), gabapentin (33%), pregabalin (31%), TCAs (25%), duloxetine (25%). The numbers of discontinuations were statistically significantly different among the six index medicines (p=0.0001). Patients who started with pregabalin had the highest percentage of switching to another medication (7%), followed by patients who started with lidocaine (6%), TCAs (5%), gabapentin and duloxetine (3%), opioids (2%). The numbers of people switching were statistically significantly different among the six index medicines (p=0.0001). Patients who started with duloxetine had the highest percentage of adding on another medication (8%), followed by patients who started with TCAs (6%), opioids (5%), pregabalin and lidocaine (4%), gabapentin (3%). The numbers who added on were statistically significantly different among the six index medicines (p=0.0001). Patients who started with duloxetine also had the highest percentage of staying on the same treatment (68%), followed by patients who started with TCAs (64%), gabapentin (60%), pregabalin (58%), lidocaine (43%), opioids (42%). The numbers of nonswitching were statistically significantly different among the six index medicines (p=0.0001) (Table 3.9).

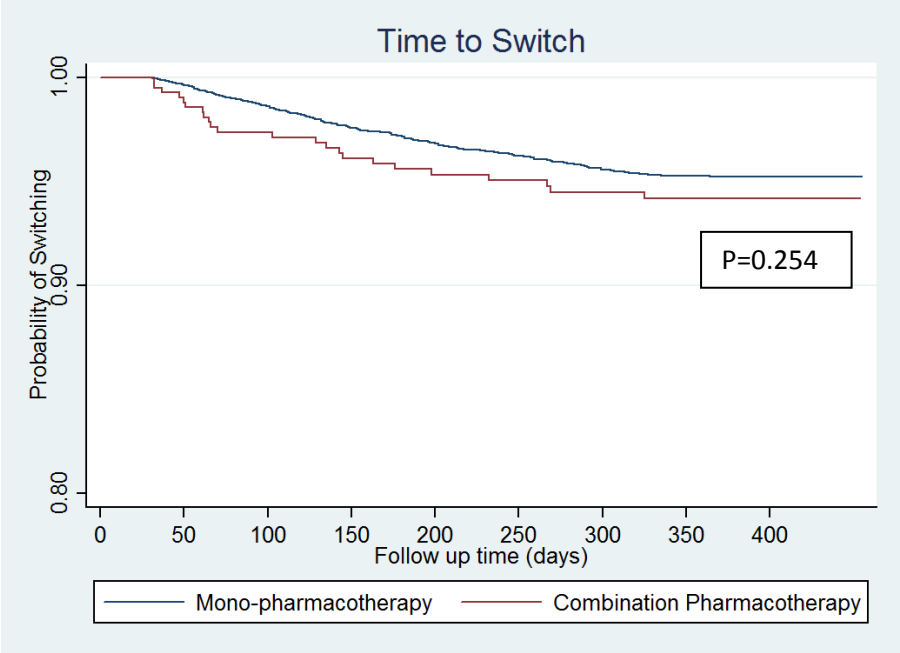


Figure 3.4 Kaplan-Meier Curve of Time to Switch Among Different Treatment Groups

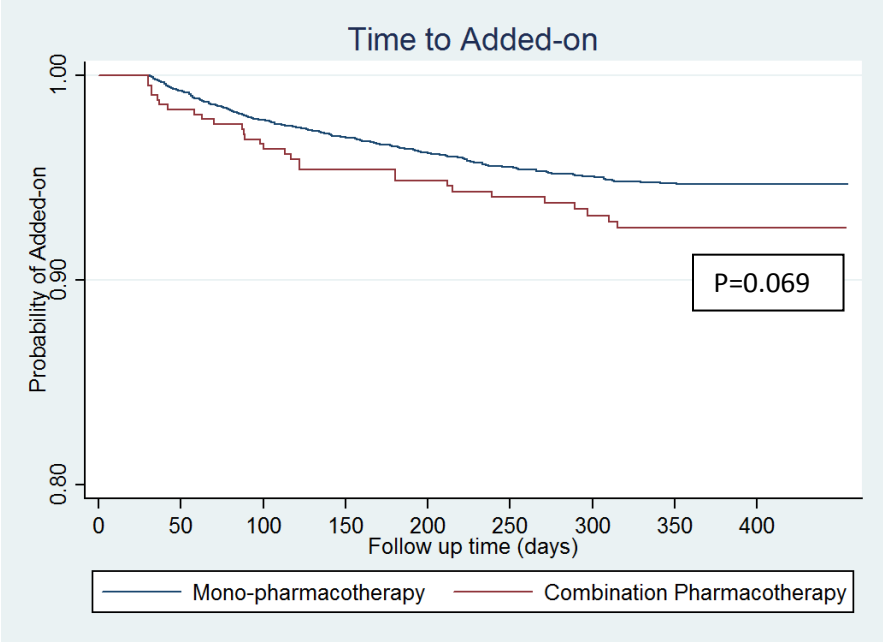


Figure 3.5 Kaplan-Meier Curve of Time to Add on Among Different Groups

Table 3.9 Patient Distribution in Index Medicine Among Different Mono-pharmacotherapy Treatment Groups

Index Medicine	Discontinue		NonSwitch		Switch		Add-on		Total
	N	%	N	%	N	%	N	%	N
Pregabalin	283	31%	536	58%	61	7%	40	4%	920
Gabapentin	1319	33%	2403	60%	124	3%	134	3%	3980
Duloxetine	82	21%	262	68%	12	3%	29	8%	385
Opioids	476	51%	390	42%	19	2%	51	5%	936
TCAs	208	25%	525	64%	38	5%	46	6%	817
Lidocaine	52	49%	46	43%	6	6%	3	3%	107
Total	2420	34%	4162	58%	260	4%	303	4%	7145

Opioids: tramadol, oxycodone, morphine, oxymorphone, methadone, levorphanol, hydrocodone, hydromorphone; TCAs: amitriptyline, desipramine, nortriptyline

Figure 3.6 shows from 2006 to 2012, more patients used gabapentin and opioids in 2012 than in 2006. Fewer patients used TCAs, pregabalin, and duloxetine in 2012 than in 2006; however, there was no difference in the usage of lidocaine from 2006 to 2012.

Among patients who discontinued in the mono-pharmacotherapy, patients who were treated with opioids were 2.78 times as likely to discontinue as patients with TCAs (95% CI: 2.3-3.2, $p<0.001$), followed by lidocaine (HR: 2.49, 95% CI: 1.8- 3.4, $p<0.001$), gabapentin (HR: 1.34, 95% CI: 1.2-1.6, $p<0.001$), and pregabalin (HR: 1.25, 95% CI: 1.0-1.5, $p=0.016$). Patients who started with an opioid had the shortest treatment before discontinuation, which was a mean of 47.3 days, and patients who started with duloxetine had the longest treatment before discontinuation, which was a mean of 91.5 days (Table 3.10; Figure 3.7).

Among patients who switched to another medication in the mono-pharmacotherapy group, patients who were treated with pregabalin were 1.55 times as likely to switch as patients with TCAs (95% CI: 1.0-2.3, $p=0.035$). Patients who were

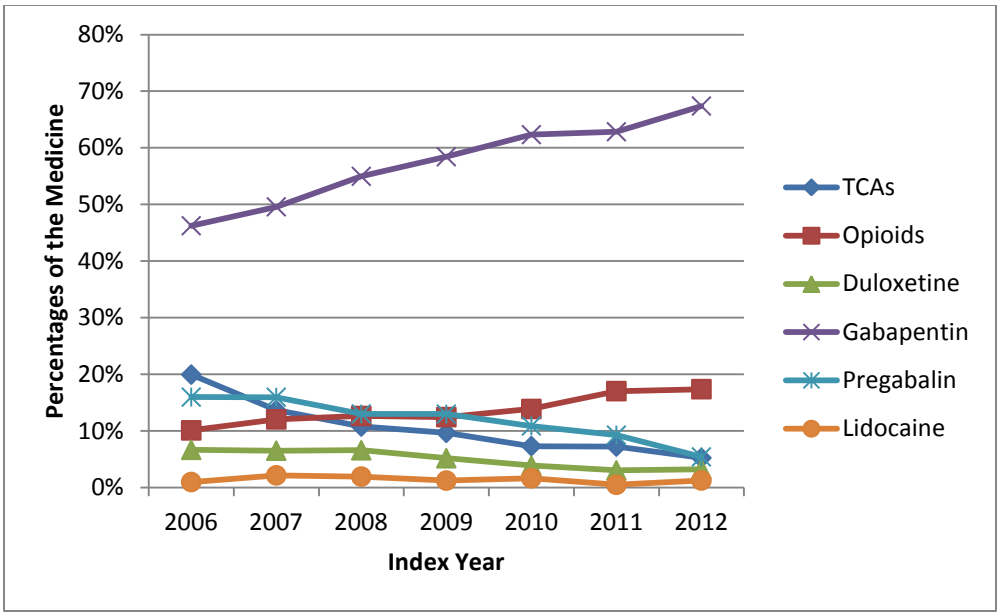


Figure 3.6 Treatment Patterns for Mono-pharmacotherapy Patients from 2006-2012

treated with gabapentin were 0.68 times as likely to switch as patients with TCAs (95% CI: 0.5-1.0, p=0.038), followed by opioids (HR: 0.5, 95%CI: 0.3-0.9, p=0.014). Patients who were treated with opioids took the longest time to switch to another medication, which was a mean of 170.3 days, and patients who were treated with lidocaine took the shortest time to switch to another medication, which was a mean of 93.2 days (Table 3.10; Figure 3.8).

Among patients who added on to another medication in the mono-pharmacotherapy group, patients in the gabapentin group were 0.59 times as likely to add on as patients with TCAs (95% CI: 0.4-0.8, p=0.002). Patients who began with duloxetine took the shortest time to add on another medicine, which was a mean of 102.2 days, and patients who began with lidocaine took the longest time to add on another medicine, which was a mean of 102.2 days (Table 3.10; Figure 3.9).

Table 3.10 Switching, Add-on, and Discontinuation of Therapy of Index Medicine

	Pregabalin	Gabapentin	Duloxetine	Opioids	TCAs	Lidocaine
Discontinue (N)	283	1319	82	476	208	52
Days to discontinuation, mean (median)	86.2 (69)	81.9 (60)	91.5 (87)	47.3 (30)	69.0 (53)	63.2 (30)
HR, (95% CI)	1.25 (1.0-1.5)	1.34 (1.2-1.6)	0.79 (0.6-1.0)	2.78 (2.3-3.2)	Ref	2.49 (1.8-3.4)
P value	0.016	<0.001	0.067	<0.001	Ref	<0.001
Switch (N)	61	123	12	19	38	6
Days to switching, mean (median)	150.7 (149)	144.9 (125)	125.1 (104.5)	170.3 (174)	128.0 (93.5)	93.2 (71)
HR, (95% CI)	1.55 (1.0-2.3)	0.68 (0.5-1.0)	0.61 (0.3-1.2)	0.50 (0.3-0.9)	Ref	1.64 (0.7-3.9)
P value	0.035	0.038	0.135	0.014	Ref	0.260
Add-on (N)	40	134	29	51	46	3
Days to augmentation, mean (median)	125.7 (104)	133.9 (109.5)	102.2 (76)	123.0 (97)	115.6 (89)	150.7 (169)
HR, (95% CI)	0.79 (0.5-1.2)	0.59 (0.4-0.8)	1.33 (0.8-2.1)	1.02 (0.7-1.3)	Ref	0.56 (0.2-1.8)
P value	0.265	0.002	0.230	0.904	Ref	0.331

HR: Hazard Ratio; CI: Confidence Interval

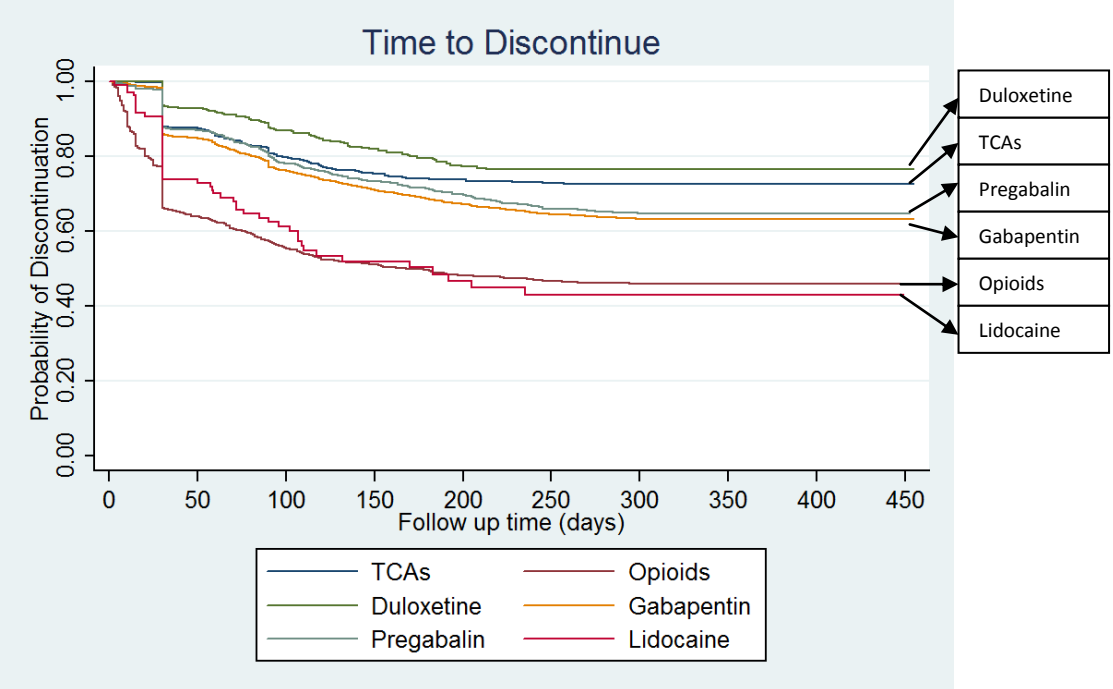


Figure 3.7 Kaplan-Meier Curve of Time to Discontinue Among Different Medicines in Mono-pharmacotherapy Group

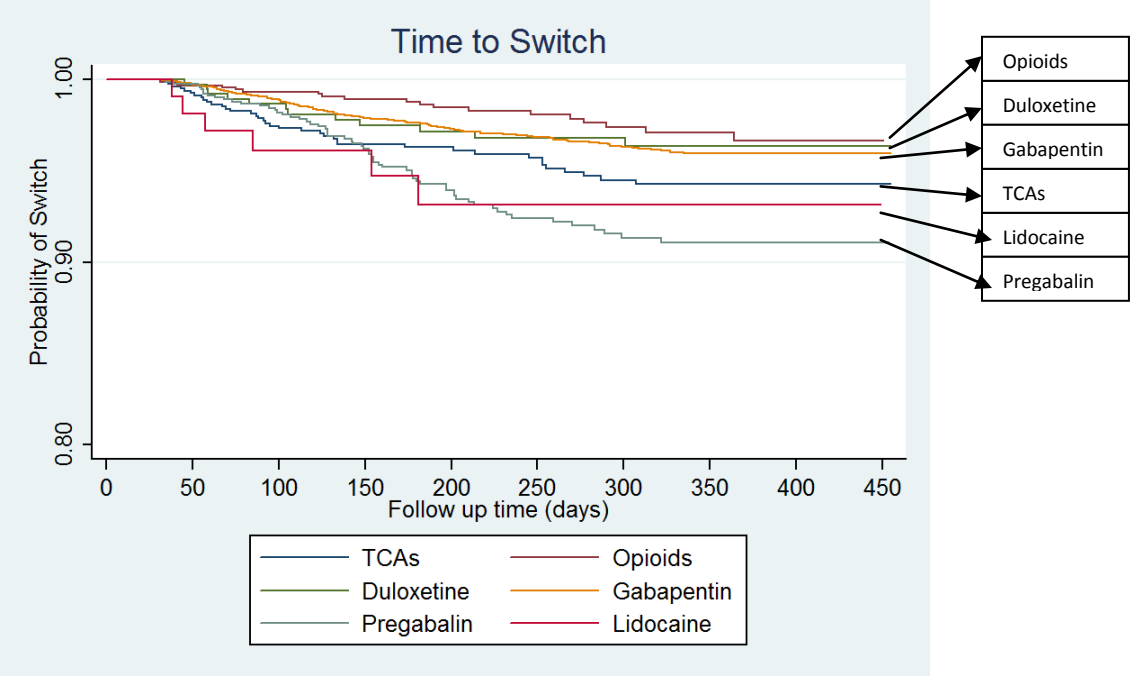


Figure 3.8 Kaplan-Meier Curve of Time to Switch Among Different Medicines in Mono-pharmacotherapy Group

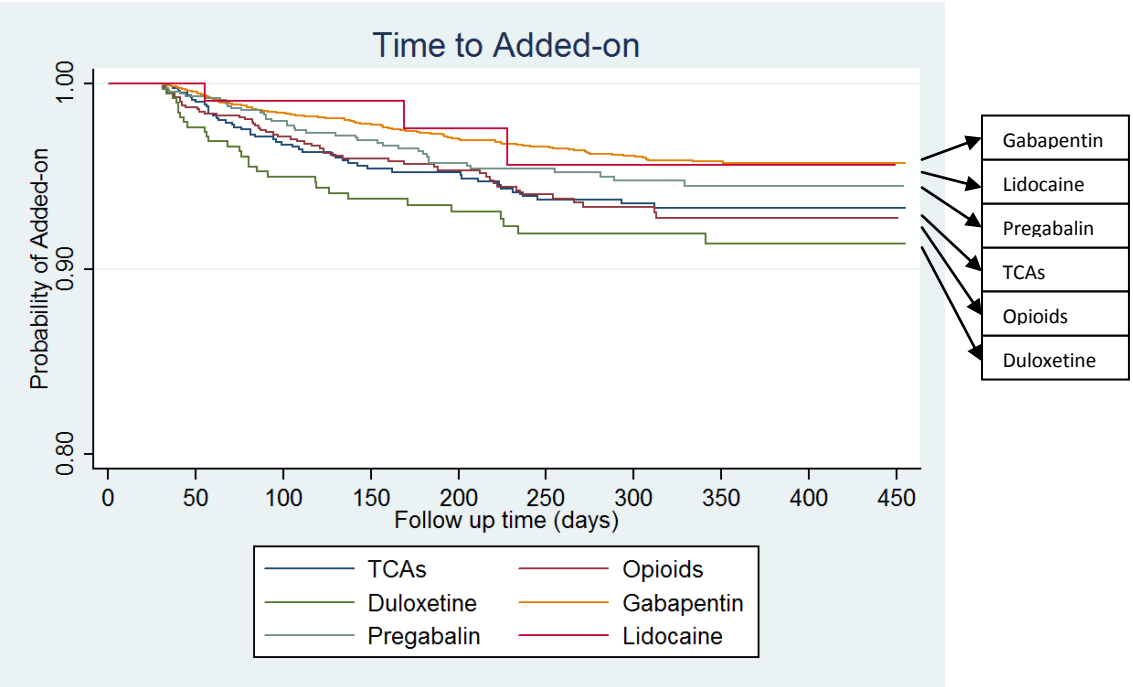
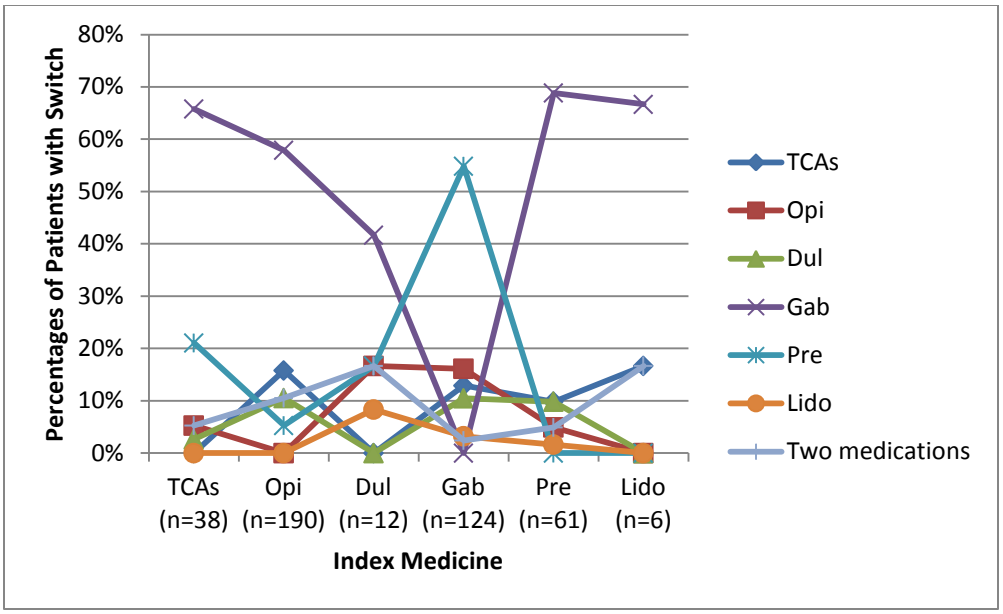


Figure 3.9 Kaplan-Meier Curve of Time to Add on Among Different Medicines in Mono-pharmacotherapy Group

Overall, there were 260 patients who switched to another medication in the mono-pharmacotherapy group. Figure 3.10 shows pregabalin patients mostly tend to switch to gabapentin (n=42, 68.9%), and gabapentin patients mostly tend to switch to pregabalin (n=68, 54.8%). If gabapentin patients do not switch to pregabalin, they tend to switch to opioids (n=20, 16.1%). Patients tend to switch between pregabalin and gabapentin because pregabalin and gabapentin are all α_2-δ subunit voltage-gated calcium channel antagonists; therefore, switching to the different medicine does not change the mechanism acted on the patients. However, the reasons of switching may be adverse effects or the cost difference between pregabalin and gabapentin (Figure 3.10).

Duloxetine (n=5, 41.7%), opioids (n=11, 57.9%), TCAs (n=25, 65.8%), and lidocaine (n=4, 66.7%) patients tended to switch to gabapentin, that is to say, other than the patients who started with gabapentin, the rest of them tended to switch to gabapentin. If duloxetine patients did not switch to gabapentin, they tended to switch to opioids, pregabalin, or another two medications, (n=2, 16.7%) which were TCAs-pregabalin combination and opioids-gabapentin combination. If opioids and lidocaine patients did not switch to gabapentin, opioid patients tended to switch to TCAs (n=3, 15.8%), and lidocaine patients tended to switch to either TCAs or duloxetine- gabapentin combination (n=1, 16.7%). If TCAs patients did not switch to gabapentin, they tended to switch to pregabalin (n=8, 21%). If pregabalin patients did not switch to gabapentin, they tended to switch to antidepressants, which was either TCAs or duloxetine (n=6, 9.8%) (Figure 3.10).

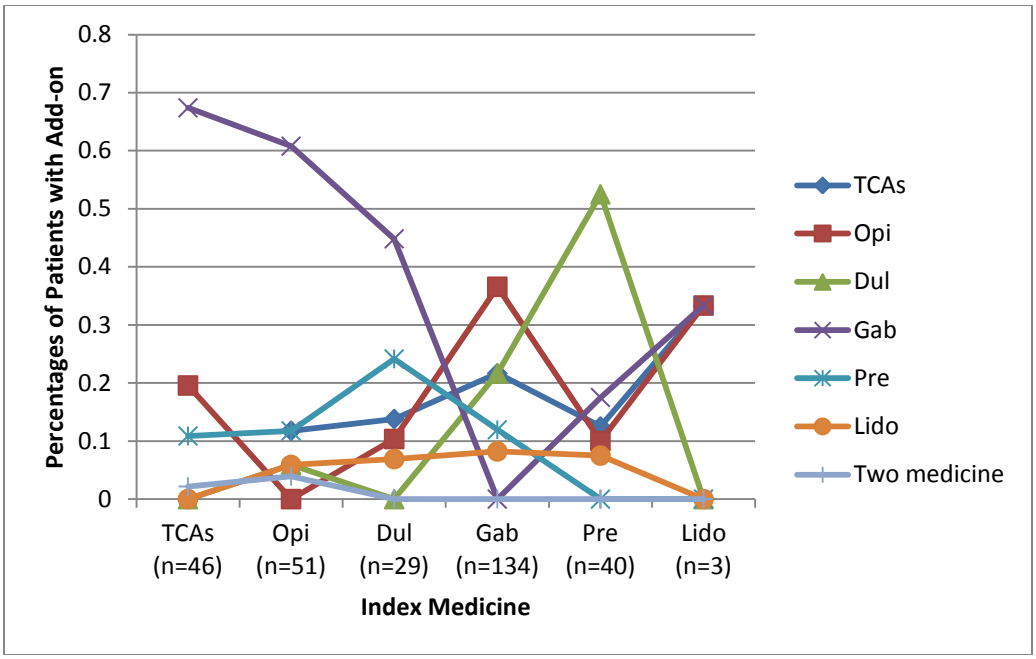
There were 303 patients who had another medication added after the index medicine in the mono-pharmacotherapy group. Figure 3.11 shows pregabalin patients



† Opi: opioids; Dul: duloxetine; Gab: gabapentin; Pre: pregabalin; Lido: lidocaine

Figure 3.10 Treatment Patterns of Mono-pharmacotherapy Patients (Switch)

mostly tend to have duloxetine (n=21, 52.5%) added to their treatments. If pregabalin patients do not have duloxetine added, they tend to have gabapentin (n=7, 17.5%) added. It seems unreasonable to add a medicine with the same mechanism: gabapentin to pregabalin; however, physicians were possibly finding the right treatment from these two medications. Gabapentin patients mostly tend to have opioids (n=49, 36.6%) added to their treatments, and if they do not have opioids added, they tend to have antidepressants added, which was either duloxetine or TCAs (n=29, 21.6%). Duloxetine (n=13, 44.8%), opioids (n=31, 60.8%), and TCAs (n=31, 67.8%) patients tended to have gabapentin added to their treatments. If duloxetine, opioids, and TCA patients did not have gabapentin added, duloxetine patients tended to have pregabalin (n=7, 24.1%) added, opioids patients tended to have either TCAs or pregabalin (n=6, 11.8%) added, and TCAs patients tended to have opioids (n=9, 29%) added (Figure 3.11).



† Opi: opioids; Dul: duloxetine; Gab: gabapentin; Pre: pregabalin; Lido: lidocaine

Figure 3.11 Treatment Patterns of Mono-pharmacotherapy Patients (Add-on)

3.2.3 Treatment Patterns in the Combination Pharmacotherapy Group

There were 421 patients who initiated treatment with two or more drugs within 30 days, representing 23 index combinations. These data are described in Table 3.11. The most common index combinations were opioids+ gabapentin (n=114, 27.1%), TCAs+ gabapentin (n=73, 17.3%), duloxetine+ gabapentin (n=36, 8.6%), opioids+ pregabalin (n=34, 8.1%), followed by the less common combinations: gabapentin+ pregabalin (n=31), TCAs+ opioids (n=20), gabapentin+ lidocaine (n=20), TCAs+ pregabalin (n=19), duloxetine+ pregabalin (n=18), opioids+ duloxetine (n=10), TCAs+ duloxetine (n=9), opioids+ lidocaine (n=9), pregabalin+ lidocaine (n=4), duloxetine+ lidocaine (n=1).

There were 23 patients with 3 medicines on the index date, and they were TCAs+ opioids + gabapentin (n=5), opioids+ duloxetine +gabapentin (n=4), opioids+

Table 3.11 Classifications of the Combination Pharmacotherapy

Index Medicine	Discontinue (N=189)		Non-Switch (N=170)		Switch (N=33)		Add-on (N=29)		Total
	N	%	N	%	N	%	N	%	
Opi +Gab	57	50%	46	40%	4	4%	7	6%	114
TCA+Gab	34	47%	32	44%	4	5%	3	4%	73
Dul+ Gab	12	33%	20	56%	2	6%	2	6%	36
Opi+ Pre	15	44%	18	53%	0	0%	1	3%	34
Gab+ Pre	24	77%	4	13%	1	3%	2	6%	31
TCA+Opi	9	45%	6	30%	0	0%	5	25%	20
TCA+ Pre	5	26%	11	58%	2	11%	1	5%	19
Dul+ Pre	6	33%	8	44%	4	22%	0	0%	18
Opi+ Dul	3	30%	3	30%	2	20%	2	20%	10
TCA+Dul	3	33%	3	33%	1	11%	2	22%	9
Any* + Lido	18	53%	10	38%	2	6%	4	12%	34
Two medicine total	186	51%	151	41%	22	6%	26	7%	364
Three medicine	13	57%	9	39%	1	4%	0	0%	23

* Opi+ Lido (n=9); Dul+ Lido (n=1); Gab+ Lido (n=20); Pre+ Lido (n=4)
† Opi: opioids; Dul: duloxetine; Gab: gabapentin; Pre: pregabalin; Lido: lidocaine

duloxetine+ pregabalin (n=4), TCAs+ duloxetine+ gabapentin (n=3), followed by the less common combinations: TCAs+ gabapentin+ pregabalin(n=2), TCAs+ duloxetine+ pregabalin (n=2), opioids + pregabalin+ lidocaine (n=1), TCAs+ gabapentin+ pregabalin (n=1), duloxetine+gabapentin+ lidocaine (n=1).

Among patients with 2 medicines at the index, patients who started with gabapentin+ pregabalin group were most likely to discontinue (77%) during the study period. Patients who started with TCAs+ pregabalin had the highest nonswitch percentage (58%), and patients who started with duloxetine+ pregabalin were most likely to switch (22%) to another medication or medications. Patients who started with TCAs+ opioids were most likely to have another medication added (25%) (Table 3.11).

From 2006 to 2012, more patients used opioids+ gabapentin in 2012 than in 2006,

and the peak was in 2011. Also, more patients used duloxetine+ gabapentin in 2012 than in 2006. However, fewer patients used TCAs+ gabapentin in 2012 than in 2006; fewer patients used opioids+ pregabalin in 2012 than in 2006, but the peak was in 2010. The usage of gabapentin+ pregabalin did not change, but the peak was in 2010 (Figure 3.12).

Among patients who started with two medications, 22 of them had switched to another two medications after the index date, and most of them switched to another two medications evenly. Patients who started with duloxetine+ lidocaine only switched to opioid+ lidocaine (n=1), and patients who started with gabapentin+ pregabalin only switched to TCAs+ pregabalin (n=1). Patients who began with TCAs+ gabapentin tended to switch to TCAs+ pregabalin (n=3). Only one of them switched to another three medicines, which was opioids+ duloxetine+ gabapentin to TCAs+ opioids+ gabapentin (Figure 3.13).

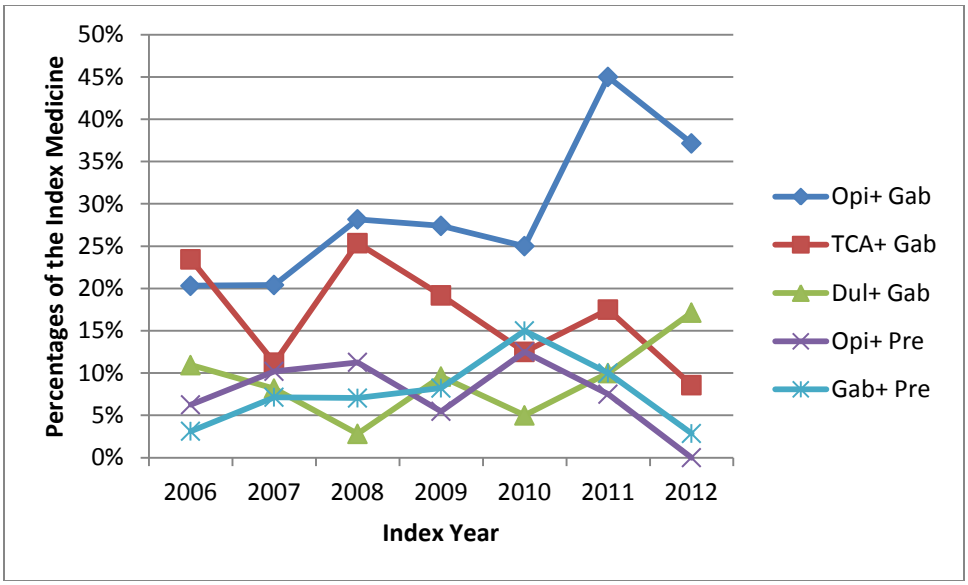
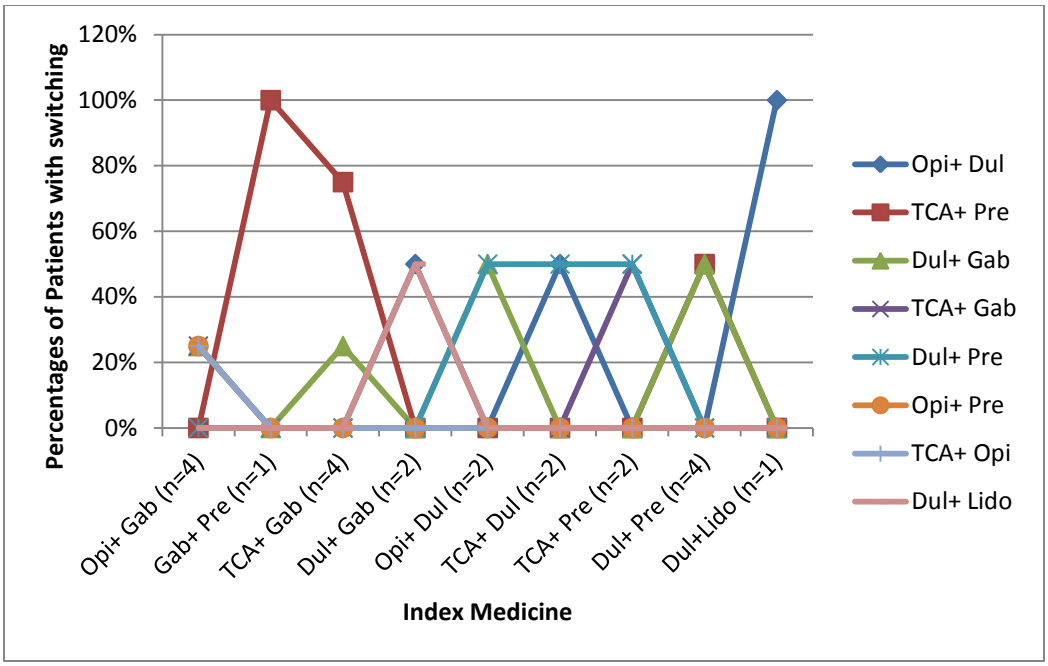


Figure 3.12 Treatment Patterns for Combination Pharmacotherapy Patients from 2006-2012



† Opi: opioids; Dul: duloxetine; Gab: gabapentin; Pre: pregabalin; Lido: lidocaine

Figure 3.13 Treatment Patterns of Combination Pharmacotherapy Patients -Switch

Among patients who started with two medications, 29 of them had another medication added after the index date. Patients who started with TCAs+ gabapentin/ pregabalin (n=4) and patients who started with duloxetine+ gabapentin (n=2) only had opioids added. Patients who began with opioids+ gabapentin/ pregabalin (n=3) and patients who began with gabapentin+ pregabalin (n=2) tended to have duloxetine (n=2) added. Patients who started with TCAs+ opioids tended to have gabapentin (n=3) added. (Figure 3.14).

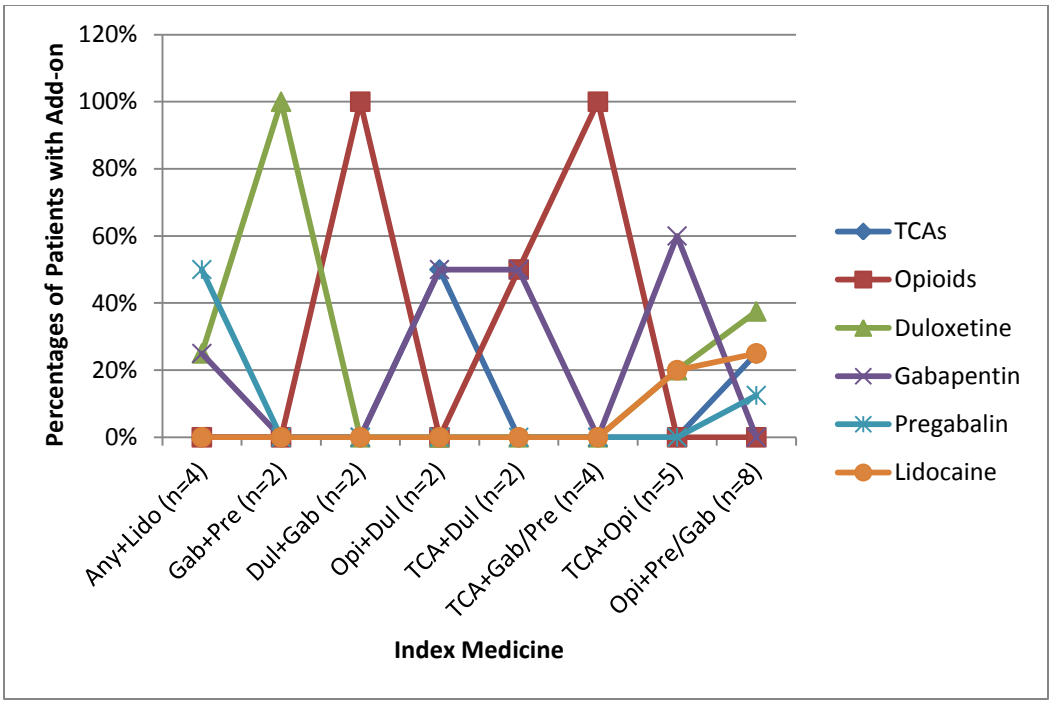


Figure 3.14 Treatment Patterns of Combination Pharmacotherapy Patients –Add-on

3.3 Predictors of Combination Pharmacotherapy in DPN Patients

3.3.1 Results Against Hypothesis 3: Demographics and Clinical Characteristics Will Affect the Likelihood of Receiving Combination Pharmacotherapy

Age, gender, insurance plan, region, and the numbers of co-morbidities were considered as predictors of receiving combination pharmacotherapy; however, there were no statistically significant differences in regions and insurance plan. Patients who were older than 65 compared to age 18- 44 (OR=0.44, 95% CI: 0.29- 0.66, p<0.001) were less likely to start with combination pharmacotherapy. Patients who were female compared to male (OR=1.25, 95% CI: 1.03- 1.55, p=0.003), with over seven co-morbidities compared to with one to four co-morbidities (OR=1.43, 95% CI: 1.09- 1.87, P=0.011), were more likely to start with combination pharmacotherapy (Table 3.12).

Table 3.12 Characteristics Associated with Combination Pharmacotherapy (demographics)

	Odds Ratio	95% CI	P value
Age			
18-44	Ref	Ref	Ref
45-65	0.75	0.52-1.08	0.128
>=65	0.44	0.29-0.66	0.000
Gender			
Male	Ref	Ref	Ref
Female	1.26	1.03-1.55	0.024
Insurance Plan Type			
Commercial	Ref	Ref	Ref
Medicaid	1.04	0.74-1.45	0.833
Medicare	0.98	0.72-1.32	0.878
Self- Insured	1.29	0.16-10.19	0.809
Missing	0.89	0.58-1.37	0.591
Region			
West	Ref	Ref	Ref
Midwest	1.44	0.98-2.11	0.061
Northeast	1.39	0.98-1.99	0.065
South	1.35	0.97-1.89	0.078
Puerto Rico	0.74	0.39-1.42	0.374
Missing	0.97	0.45-2.08	0.930
Numbers of Comorbidities			
With 1-4 comorbidities	Ref	Ref	Ref
With 5-7 comorbidities	0.97	0.77-1.22	0.793
With >7 comorbidities	1.43	1.09-1.87	0.011

Five disorders and conditions were considered as predictors of receiving combination pharmacotherapy: cardiovascular disorders, diabetes-related condition, mental disorders, sleep disorders, and musculoskeletal pain conditions. Patients who had mental disorders were more likely to start with combination pharmacotherapy than those without (OR=1.56, 95% CI: 1.24- 1.97, p< 0.001), and had musculoskeletal pain conditions than those without (OR= 1.36, 95% CI: 1.10-1.67, p=0.004). However,

patients with cardiovascular disorders were less likely to start with combination pharmacotherapy than those without (OR= 0.73, 95% CI: 0.54-0.98, p=0.037) (Table 3.13).

Among specific co-morbidity as predictors of receiving combination pharmacotherapy, only three of the 17 co-morbidities in our study had statistically significant differences. Patients who had hypertension compared to those without (OR=0.79, 95% CI: 0.63-0.99, p=0.045) were less likely to start with combination pharmacotherapy. However, patients who had depression (OR=1.59, 95% CI: 1.23-2.05, p<0.001), and arthritis (OR=1.54, 95% CI: 1.24-1.95, p<0.001) compared to those without were more likely to start with combination pharmacotherapy (Table 3.14).

3.4 Healthcare Costs of DPN Patients

3.4.1 Results Against Hypothesis 4: Patients Who Take Combination Pharmacotherapy Have Lower Medical Costs than Patients Who Take Mono-pharmacotherapy

The average total mean cost was $5,874 in the 6-month pre-index, and among all the treatment groups, patients who discontinued in the combination pharmacotherapy group had the highest 6-month pre-index mean cost: $8,527; patients who added on another medication in the combination pharmacotherapy group had the lowest pre-index mean cost: $2,280. The same as the pre-index, patients in the combination pharmacotherapy group who switched to another two medications had the highest 1-year post-index mean cost: $25,423; patients who added on another medication in the combination pharmacotherapy group had the lowest post-index mean cost: $8,514. The average of the total mean cost was $13,111 in the 1-year post-index.

Table 3.13 Characteristics Associated with Combination Pharmacotherapy (co-morbidities)

	Odds Ratio	95% CI	P value
Cardiovascular disorders	0.73	0.54-0.98	0.037
Diabetes-related condition	0.89	0.70-1.12	0.319
Mental disorders	1.56	1.24-1.97	0.000
Sleep disorders	0.95	0.67-1.34	0.750
Musculoskeletal pain conditions	1.36	1.10-1.67	0.004

Table 3.14 Characteristics Associated with Combination Pharmacotherapy (specific co-morbidities)

	Odds Ratio	95% CI	P value
Cardiovascular disorders			
Congestive heart failure	1.14	0.84-1.54	0.407
Peripheral vascular disease	1.02	0.80-1.30	0.879
Cerebrovascular disease	0.92	0.67-1.28	0.631
Coronary heart disease	0.96	0.75-1.24	0.755
Hypertension	0.79	0.63-0.99	0.045
Hyperlipidemia	0.89	0.72-1.10	0.282
Diabetes-related condition			
Retinopathy	0.86	0.61-1.19	0.360
Nephropathy	0.91	0.68-1.22	0.526
Mental disorders			
Depression	1.59	1.23-2.05	<0.001
Bipolar disorder	1.26	0.54-2.94	0.597
Anxiety	1.04	0.67-1.61	0.861
Sleep disorders			
Insomnia/sleep disorders	0.93	0.65-1.31	0.669
Musculoskeletal pain conditions			
Arthritis and other arthropathies	1.54	1.24-1.92	<0.001
Rheumatoid arthritis	0.87	0.44-1.72	0.687
Low back pain	1.39	1.10-1.75	0.005
Back and neck pain, other than low back pain	1.03	0.76-1.41	0.832
Rheumatism, excluding the back	0.94	0.76-1.17	0.577

The pre-index total costs of the mono-pharmacotherapy group were not statistically significantly lower than the combination pharmacotherapy group ($5,743 vs. $7,936, p=0.05). The post-index total costs of the mono-pharmacotherapy group were statistically significantly lower than the combination pharmacotherapy group ($12,950 vs. $15,643, p=0.02) (Table 3.15).

The cost difference is total mean post-index cost minus the total mean pre-index cost; in order to have the consistent time frame for pre- and post-index, the mean cost only included 6-month post-index cost. There was no statistically significant difference between mono-pharmacotherapy and combination pharmacotherapy group in the cost difference ($818 vs. $1,425, p=0.63) (Figure 3.15).The lowest cost difference was patients in combination pharmacotherapy group who stayed on the same treatment ($ -1,901), and the highest cost difference was patients in combination pharmacotherapy group who switched to another two medications ($ 9,499) (Figure 3.16).

Table 3.15 Total Mean Costs Among Treatment Groups

	Mono-Pharmacotherapy				Combination Pharmacotherapy			
	Discontinue ($)	Non-Switch ($)	Switch ($)	Add-on ($)	Discontinue ($)	Non-Switch ($)	Switch ($)	Add-on ($)
Pre-index (6 month)	5,309	6,045	3,805	7,147	8,527	8,263	2,877	2,280
Post-index (1 year)	12,644	12,831	11,891	18,899	20,881	9,505	25,422	8,515

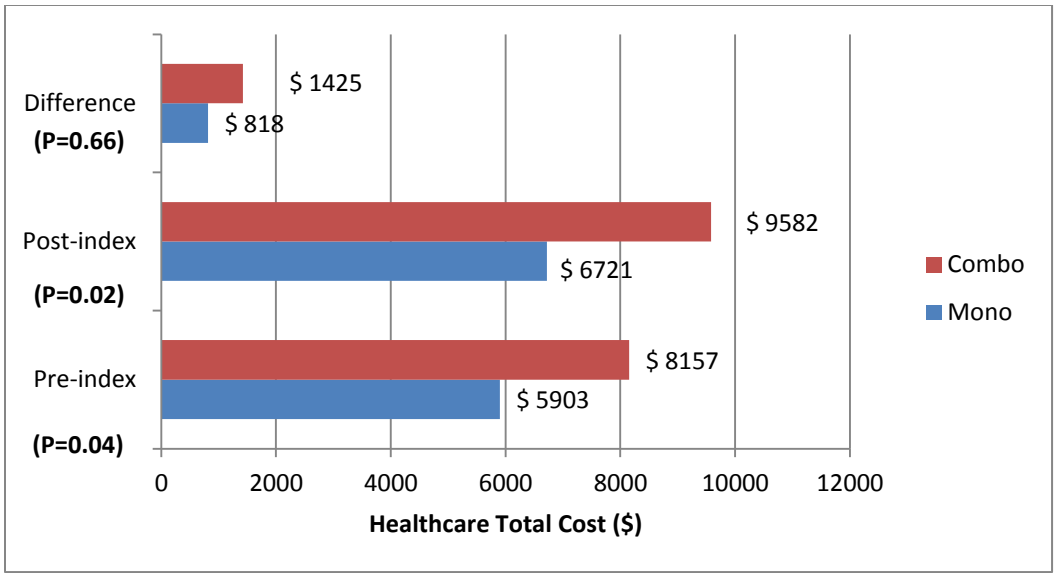


Figure 3.15 Total Mean Costs Between Mono-pharmacotherapy and Combination Pharmacotherapy

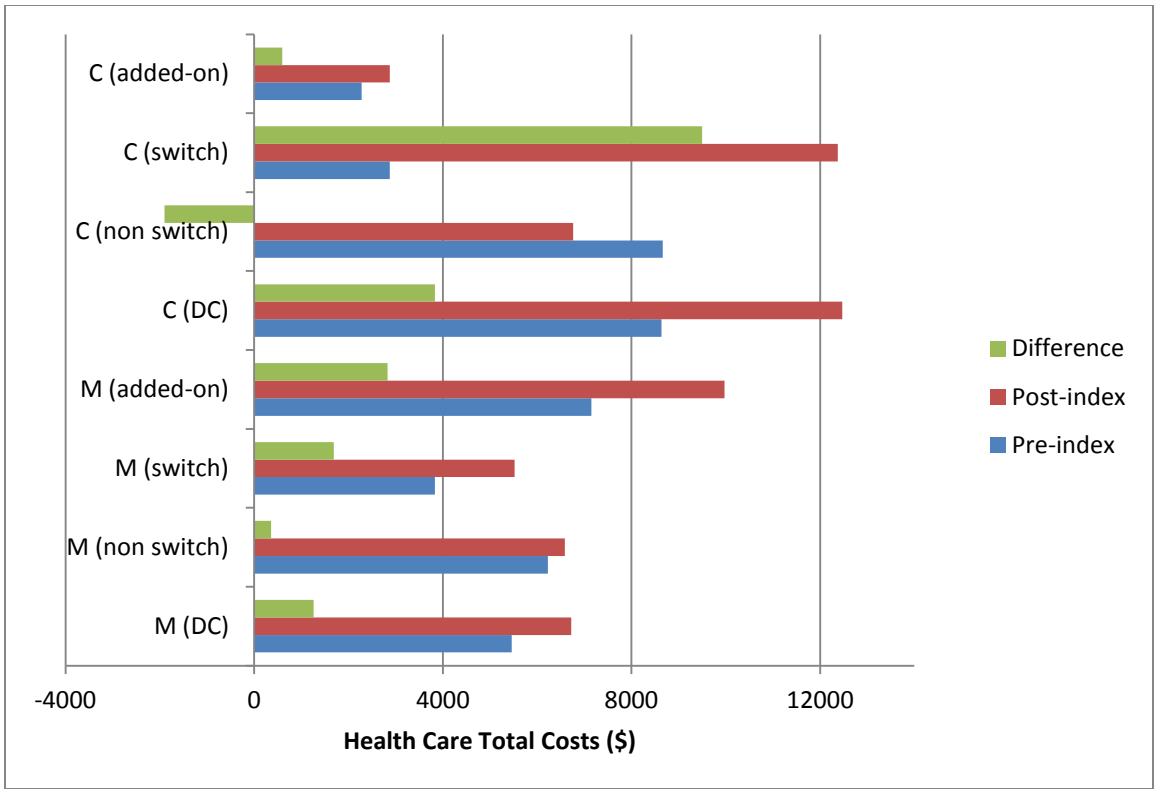


Figure 3.16 Total Mean Costs Among Treatment Groups

CHAPTER 4

DISCUSSION

4.1 Summary of Study Findings

Based on the IOM report: Relieving Pain in America, the US spends at least $560 to $635 billion annually on chronic pain.[77] DPN patients are included in chronic pain patients, whose pain can cause them not go to work when symptoms are present, lose sleep, or require caregivers to take care of their daily life. According to the literature, DPN patients are under treated, and for those who are treated, many of them cannot control their pain well even when they take their medicine with good adherence. Since many DPN patients are not being effectively treated, it leads to additional office/ ER visits and higher healthcare costs. In order to find the optimal treatment for newly-treated DPN patients, the current study is designed to quantify DPN treatment patterns, determine the types of combination pharmacotherapy, describe the co-morbidities, determine the predictors of the patients who received combination pharmacotherapy, and compare healthcare costs between mono-pharmacotherapy and combination pharmacotherapy.

The results showed the proportion of mono-pharmacotherapy (94.4%) was much higher than combination pharmacotherapy (5.6%). The percentage of mono-pharmacotherapy in this study was much higher than combination pharmacotherapy

compared with literature, which may be related to the majority of the study population being newly-treated patients. Gore et al. reported that 52.2% of DPN patients took at least two prescription medications,[22] but the patients in the study had used pain medications an average of 5.4 years, which was different from this cohort where everyone was newly-treated. Another reason for the difference is the definition of the combination pharmacotherapy. Hall et al. investigated newly-treated patients and reported that 16.9 % of DPN patients used at least two medications.[25] However, the days of the prescription filled and the overlap periods of two medications were not described, and it is possible that they do not have any overlap periods or have a really short one. Even though a 10-day overlap of two prescriptions can be considered as using two medications, it is more for short-term rescue, which is not the purpose of this study. The purpose of this study is to define the optimal combination pharmacotherapy for newly-treated DPN patients. On the other hand, each medication had at least a 60-day prescription fill and a 60-day overlap in this cohort. The last reason for lower combination pharmacotherapy in this cohort is that only DPN guideline-suggested medications were investigated, whereas in the literature both OTCs and NSAIDs were included. Even though the proportions of patients who take combination pharmacotherapy seem small in this study, the strict definitions, newly-treated patients and only including guideline-suggested medications might be the reason for the number differences.

This study showed that once patients are on combination pharmacotherapy they are more likely to discontinue from index medications. The addition of a new medication or switching is no different for either group, so it seems that adding on another medicine or switching is a more inevitable step, regardless of whether patients initiated mono-

pharmacotherapy or they were already on combination pharmacotherapy. In other words, whether the DPN patients started with mono- or combination pharmacotherapy, the first treatment is ineffective, and both mono- and combination pharmacotherapy patients are likely to fail. However, this conclusion is from the treatment patterns, not the pain scales, which is more standard to define treatment efficacy. Overall, the study disproves the hypothesis that patients who take combination pharmacotherapy for DPN are less likely to discontinue, switch, or add on therapy than patients who take mono-pharmacotherapy. This may be related a higher priority control blood pressures and blood sugars, and thus the symptoms of pain seem less important; therefore, patients who start with combination pharmacotherapy tended to discontinue from two medications to one medication.

TCAs, duloxetine, gabapentin, and pregabalin are recommended as the first-line treatment in TEPDN,[39] NeuPSIG,[35] and EFNS guidelines.[36] Gabapentin was the most commonly prescribed medication as the index medicine in this cohort (55.7%), followed by opioids (13.1%), pregabalin (12.9%), TCAs (11.4%), duloxetine (5.4%), and lidocaine patch (1.5%). Even though gabapentin is not an FDA approved medication for DPN, it is the most commonly prescribed medicine in this cohort.[109] The same results were also shown in the Chen et al. study when compared with duloxetine, TCAs, venlafaxine, pregabalin, and opioids, gabapentin is also prescribed most commonly.[97] Opioids are not the first-line treatment in any of the DPN guidelines, but they are the second most commonly prescribed medication in this cohort. Physicians might prescribe them as a rescue medicine. In contrast, duloxetine is not being prescribed commonly in our study, which is aligned with UK cohort study that duloxetine and venlafaxine were prescribed in fewer than 2 % of DPN patients.[25] Opioids+ gabapentin (27.1%), TCAs+ gabapentin

(17.6%), and duloxetine+ gabapentin (8.6%) are the most common combination groups in our study; noticeably, all the top three groups included gabapentin. Since this is the first observational study to investigate combination pharmacotherapy in DPN patients, there is no literature to prove or disapprove this result.

Patients who started with duloxetine had the highest nonswitch percentages (68%), and Zhao et al. also showed duloxetine had better adherence compared with pregabalin.[98] Patients who started with TCAs-pregabalin combination had the highest nonswitch percentage (58%) compared with other combinations. Among patients with two medicines on the index date, patients who started with pregabalin and gabapentin were most likely to discontinue (77%). It makes sense that patients who start with gabapentin and pregabalin have the highest discontinue percentage, for physicians might prescribe both of them at first, and then discontinue one of the medications after, since pregabalin and gabapentin have the same mechanism or could be step therapy for using gabapentin first then pregabalin. Among all the medication, opioids discontinued in the shortest time (Median: 30 days), and had the highest discontinuations than other medications (51%). It demonstrates that opioids cannot be used in the long-term due to adverse effects, and the concerns about patient addiction. Even though it is recommended in guidelines to use gabapentin and opioids after the first-line treatment failure, [39] physicians should prescribe them with caution for opioids might increase risk of serious harms that appear to be dose-dependent. Compared to patients who started with opioids, lidocaine, gabapentin, and pregabalin, patients who started TCAs are statistically significantly less likely to discontinue, which is similar to the recommendations in the review conducted by Dr. Lipman, that desipramine is the best medication to treat DPN.[117]

The recommended next steps after first-line treatment are suggested from guidelines as follows: change to another first-line agent; change to second-line agent; or add a different first- or second-line agent.[35] However, in this cohort patients who either switched or added on after the initial treatment were only in a small proportion in the mono-pharmacotherapy group, which is 4%. Patients who started with pregabalin mono-pharmacotherapy had the highest switch proportion than other medications (7%), and patients who started with duloxetine and pregabalin were most likely to switch (22%) compared to other combinations. Other than changing to another first-line agent, the guideline also suggests adding a different first- or second agent. In this study patients who started with duloxetine had the highest proportions to add on another medication (8%), and for patients in the combination pharmacotherapy group, 25% of patients who started with TCAs and opioids added on another medication. Overall, most patients in the mono-pharmacotherapy group tended to add on gabapentin, which is aligned with what the guidelines suggest: TEPDN guideline recommends to use gabapentin and opioid,[39] and EFNS guideline recommends to use gabapentin and nortriptyline after the first treatment failure.[36]

Treatment patterns of mono- and combination pharmacotherapy show that physicians tend to prescribe mono-pharmacotherapy first, that gabapentin is the most commonly prescribed medicine, the most common medicine to be switched to and to be added on, and all the top three combination groups included gabapentin. The results are surprising, since pregabalin has better pharmacokinetics, only needs to be taken twice daily, and with not much cost difference. Furthermore, even though patients who used TCAs and duloxetine have the higher percentage of nonswitch, the result showed that

fewer physicians prescribed them as first-line treatment. Future study could explore the reasons for physicians' prescribing patterns in DPN patients. The study also reported that there is a statistically significantly difference in regions between mono- and combination pharmacotherapy group, which is aligned with the McDonald et al. study:[118] they concluded that there are residual geographic variation in opioid prescribing. There is also a statistically significantly difference in insurance between mono- and combination pharmacotherapy group. Guo et al. used Medical Expenditures Panel Survey (MEPS) to examine the role of insurance type in the selection of antihypertensives, and it also showed the statistically significantly difference in insurance among different treatments. Patients with health maintenance organization insurance were less likely than fee for service (FFS) patients to follow the US Joint National Committee (JNC) guidelines; patients with all other public insurance and no insurance were not statistically different from the FFS group of following JNC guidelines[119]

Patients who took combination pharmacotherapy had more co-morbidities than patients who took mono-pharmacotherapy, and they had more mental disorders and musculoskeletal pain condition in all study periods, and more sleep disorders after they took DPN medication. This demonstrates the hypothesis is true that patients who take combination pharmacotherapy have more co-morbidity. The study also proved that demographics and clinical characteristics will affect the likelihood of receiving combination pharmacotherapy. Patients who were female compared to male, who had more than seven co-morbidities compared to less than five co-morbidities, who had depression, arthritis compared to those without, were more likely to start with combination pharmacotherapy. In contrast, patients who were older than 65 compared to

age 18 to 44, who had hypertension compared to other co-morbidities, were less likely to start with combination pharmacotherapy. Since this is the first observational study for comparing combination and mono-pharmacotherapy in newly-treated DPN patients, there is no available literature to confirm these results. However, Manteuffel et al. evaluated the differences between women and men in medication use reported that women were prescribed more medications than men,[120] which can possibly lead to our results that females are more likely to start with combination pharmacotherapy. Bluher et al. used a questionnaire to evaluate the impact of pill burden found patients who were older than 65 years old took more medications than those who were younger,[121] which may explain why our older patients would be less likely to take combination pharmacotherapy. Because the pill burden is higher in the elderly, to prescribe two medications initially for their pain symptoms would be improbable.

The annual mean cost is $13,111 in post-index, which is much lower than in the literature: $30,000 from either Pharmetrics [21, 93] or MarketScan database.[94, 97, 101] The demographic distribution and co-morbidities were not much different between our cohorts and previous literature. The reason for the big difference in annual healthcare costs might be due to only 30% of the cohort having cost data, compared to MarketScan and Pharmatrics which have almost 100% cost data. Even though cost is only calculated for patients who have cost data, the reasons healthcare costs were still lower might be due to the missing data.

In the prior 6 months to starting DPN medication, patients who started with combination pharmacotherapy and then added on another medication had the lowest pre-index mean cost: $2,280. This indicates that the less the medication burdens in pre-index,

the more likely the patients who start with combination pharmacotherapy will add on another medication. The reason will be the same as older patients being less likely to take combination pharmacotherapy initially. Since the older patients have more pill burden, patients who have less pill burden are more likely to start with combination pharmacotherapy and to add on another medication later. In both pre- and post-index, patients who discontinue combination pharmacotherapy had the highest cost, which shows that poor adherence leads to high healthcare costs, and it follows the Wu et al. study which reported that the lowest duloxetine compliance group had the highest healthcare costs.[104] Both in mono- and combination pharmacotherapy group, patients who stayed on the treatment had the lowest cost difference from post-index to pre-index, implying better adherence has the lowest costs.

The pre-index total costs of patients who started with mono-pharmacotherapy were not statistically significantly lower than patients who started with combination pharmacotherapy, but it was statistically significantly lower than patients who started with combination pharmacotherapy in the post-index, which is disproving the hypothesis that patients who take combination pharmacotherapy will have lower healthcare cost. However, patients who started with combination pharmacotherapy had more co-morbidities, and the literature showed that the higher numbers of the co-morbidities will lead to the higher costs. Therefore, patients who start with combination pharmacotherapy group will have higher costs. Even though it is disproving the hypothesis, the cost difference showed there was no statistically significant difference ($818 vs. $1,425, p=0.66) between patients who started with mono- and combination pharmacotherapy.

4.2 Discussion and Implication of Study Findings

This is the first published observational study to investigate combination pharmacotherapy usage in DPN patients. Even though the sample size of the combination pharmacotherapy patients is small (n=421), the descriptive results are still important. Based on the mechanism approach and the multiple symptoms of each DPN patient, combination pharmacotherapy might be the only effective way to treat DPN patients.[67] The results showed that patients who were older and had hypertension would be less likely to receive combination pharmacotherapy. This may because the older patients have the higher likelihood of having drug-drug interaction,[122] and hypertensive patients need to take antihypertension medications at the same time. The fact that DPN patients frequently take multiple medications may also cause fewer physicians to prescribe combination pharmacotherapy for them. Also, it is common for physicians to prescribe initial treatment first, then add on another medicine later. In our cohort, the combination pharmacotherapy is defined as having two or more medications within first 30 days. Since the result has shown taking combination pharmacotherapy would not cost more money if considering the pre-index cost, it is recommended to add on another medication sooner than 30 days if there is inadequate response. Moreover, as a result of increasingly used and implementation of patient report outcome into trials and healthcare strategy,[123] it is important to understand whether patients prefer to treat their pain symptoms rather than blood pressures or blood sugars, and will the physicians be willing to treat a patient's pain symptoms first if the patient has this preference?

Patients who were female, with more than seven co-morbidities, and had depression, arthritis were more likely to take combination pharmacotherapy. Future

research could investigate whether initial combination pharmacotherapy be more effective in patients with depression or arthritis. If the hypothesis is true, then the physicians should prescribe combination pharmacotherapy to them initially.

There were only 58% of the patients who had stayed on the same treatment in mono-pharmacotherapy group, and there were only 40% of the patients who stayed on the same treatment in combination pharmacotherapy group. It is suggested that the DPN medications remain unsuccessful to DPN patients based on the treatment patterns. More comprehensive pain registries need to be developed to create more cohort studies and find a better analgesic or a better combination regimen for DPN patients, and in the meantime patients need to learn a better coping strategy for their pain conditions.

The literature has described that multiple co-morbidities is normal for DPN patients, which may make our co-morbidities results insignificant. However, comparing the co-morbidities between patients with combination and mono-pharmacotherapy has never been done. Patients who take combination pharmacotherapy had more co-morbidities, and patients with mental disorders and other pain conditions were more likely to take combination pharmacotherapy. However, how different co-morbidities lead to different combination regimens, and which regimens are the most effective in terms of demographic and clinical characteristics should be explored in future research. Because in this cohort all the combination regimens were combined to combination pharmacotherapy, it is clear that each regimen is different; therefore, it is worthwhile to investigate the characteristic differences between regimens, and their safety and efficacy.

The study also found out patients who stay on the same treatment would have the lowest cost, which indicates that better adherence would lead to lower costs. Stone et al.

concluded there are the discordances between evidence and public policy in atrial fibrillation patients, and the reasons are variance with national guidelines and the funding restrictions for evidence-based therapies.[124] The same problems exist in DPN patients; there are no standardized guidelines for DPN,[41] there is step therapy and prior authorization to restrict the usages of evidence-based therapies. Therefore, it is hard for providers to adhere to clinical guidelines. Waddimba et al. reported providers who had the support from peers and who perceived financial rewards for quality care would have better adherence to the guidelines.[125] Pozniak et al. presented physicians do not have enough reimbursements for their diabetic care.[105] Future implications would be to provide more reimbursements for physicians, having a consistent clinical guideline to help policy makers, and considering medication costs for reimbursing DPN medications.

4.3 Limitations, Conclusions, and Recommendations for Future Research

This study only included newly-treated patients and having only one year follow-up, which may not be the best study design for a chronic disease. However, in order to thoroughly compare mono-pharmacotherapy with combination pharmacotherapy in DPN patients, it is necessary to stratify them on their first DPN prescription. The hypothesis therefore can be tested: Do patients who start with combination pharmacotherapy more easily discontinue, add on, or switch than patients who start with mono-pharmacotherapy? How is the time to discontinue, add on, or switch different from mono-pharmacotherapy and combination pharmacotherapy?

Classification bias is possible given the way patients were classified. Four treatment pattern groups were categorized in this study: discontinue, nonswitch, switch,

and add-on. It was required only that medication added on another medication for 60 days, not for the entire follow-up. The same requirements were followed with the switch group: the switch medicine might only be switched for 60 days. Even if it switched back to the original medicine afterwards, this still counted a patient as part of the switch group. Additionally, since only the first sequence of medication had been captured, the patient might switch to another medication for 60 days then add on to the same medication for 180 days; however, as a group it was still counted as the switch. Even though in reality there are flaws in this categorization, this is the most detailed and precise methodology described in the literature. Each group is mutually exclusive, and no patient has been excluded if the patient has at least a 60-day prescription filled in any DPN medication. The patterns have been described, including the index medicine, the second medicine, and the time to the first medication change. The definition of the switch or the add-on group might be different from clinical practice, but both combination and mono-pharmacotherapy patients were included. For better comprehensive overview of the DPN treatment patterns, future study should also include multiple treatment sequences and have more strict requirements for the switch and the add-on group.

Not all the guidelines suggested DPN medications are included in this study. NSAIDs or other over-the-counter (OTC) medications are not included. Patients might take other analgesics at the same time, but they are not being considered for combinations. However, the purpose of this study is to see the characteristics and optimal combination pharmacotherapy for newly-treated patients with DPN. OTC medications or other analgesics are not effective in DPN patients; therefore, it is not considered. In this study, tramadol, oxycodone, morphine, oxymorphone, methadone, levorphanol, hydrocodone,

and hydromorphone were counted as a single opioids category. That is to say, if patients used any of these opioids during study time, it was counted as continue, even with change to different kinds of opioids in between. The same issue is seen with TCAs; amitriptyline, desipramine, and notriptyline are all counted as TCAs. Future research may categorize opioids into immediate-release opioids and long-act opioids. TCAs could be separated into secondary amine and tertiary amine.

The parameters included in this study are insurance type, region, age, sex, and co-morbidities, which are not comprehensive. Other parameters that would be worth investigating are the adherence, severity of diabetes, socioeconomic characteristics, provider characteristics, and medication history. Those parameters all have impact on the treatment choices, and the treatment patterns. To include them would help to categorize DPN patients more specifically, and to determine the predictors of the different treatment groups more precisely. Admittedly, a future study could investigate how those demographic and clinical characteristics affect each combination regimen, whereas this study only investigated between mono- or combination pharmacotherapy groups.

The excluded patient numbers for each inclusion criterion are captured in the flowchart; however, many patients are missing cost data. Since Inovalon is a healthcare technology company, it does not require clients to provide cost data originally. Imputation might be a strategy; however, due to the massive amounts of the missing data and because the overall cohort patient characteristics are different from the with-cost cohort, it was not considered appropriate. Therefore, further research should consider the limitations of the cost data in Inovalon, and the validation of the database is encouraged to be done.

Overall, patients who were older than 65 and those with hypertension were less likely to start with combination pharmacotherapy. Female patients, with more than seven co-morbidities, and who had depression or arthritis were more likely to start with combination pharmacotherapy. Patients who take combination pharmacotherapy are more likely to discontinue, having more co-morbidities, and more healthcare costs than patients who take mono-pharmacotherapy. In order to offer better treatments to DPN patients, future study should look at each combination regimen, and tailor them to different patient characteristics. Because all first-line medications have similar efficacy, it is encouraged to consider cost for the treatment decision; therefore, gabapentin and TCAs will be the recommended medications. Because taking combination pharmacotherapy would not cost more money if considering the pre-index costs, it is recommended to add on another medication within 30 days. The policy maker can reimburse either gabapentin+ opioid or TCA+ gabapentin if condition is allowed. In conclusion, newly-treated DPN patients should add on another medication after initiating therapy sooner than 30 days when considering using combination pharmacotherapy.

APPENDIX

A.1 Terminology

- Index date: the first prescription filled for DPN drug during the identification period.
- Index Medicine: Medicine used on the index date, including following: TCAs, Opioids, Duloxetine, Gabapentin, Pregabalin, any route Lidocaine, and any of the combinations.
- Mono-pharmacotherapy: Patients who take only one DPN medicine on the index date. Those receiving mono-pharmacotherapy with duloxetine or pregabalin or gabapentin or amitriptyline or desipramine or notriptyline or tramadol or oxycodone or morphine, or any route lidocaine.
- Combination pharmacotherapy: Patients who are on two or more agents within 30 days after initiation of therapy with a single agent. Those receiving multiple combination therapy with gabapentin+opioids, gabapentin+notriptyline or any other combinations for listed medication. The multiple combination therapy group would be patients who are on two or more agents within 30 days after initiation of therapy with a single agent.
- Treatment groups: discontinue, nonswitch, switch, and add-on
    - Discontinue group: Patients who have a gap $\geq$ 60 days during study period will be defined as a discontinue group. If patients switched or added on another medicine after the gap, the patient would still be categorized into

- discontinue group.
- Nonswitch group: Patients without any ≥ 60-day gap continued to have the same index medicine for at least 60 days, and did not have any medicine added on in following study period.
- Switch group: Patients without any ≥ 60-day gap switched to another medicine, and the second medicine was taken for at least 60 days. Patients might switch from one medicine to two classes of medicine, or from two classes of medicine to one medicine, or switch from one to another one, two to another two.
- Add-on group: Patients without any ≥ 60-day gap added on another medicine, and the index medicine and add-on medicine needed to be overlapped at least 60 days.

- The date of discontinuation: The end date (fill date + days supply) of the last prescription prior to discontinuation was designated.
- Days to discontinuation were calculated as the number of days from the fill date of the index prescription to the end date of the last prescription prior to discontinuation.
- Days to therapy switching were calculated as the number of days from the fill date of the index medicine to the fill date of the first prescription for the switched therapy.
- Days to therapy augmentation were calculated as the number of days from the fill date of index medicine to the fill date of the first prescription for the augmented therapy.

A.2 Comparison Between Overall and With-cost Data

There were 2,478 patients having cost information before and after index-date. There were more combination pharmacotherapy patients in with-cost than the overall group (6.1% vs. 5.6%). Among mono-pharmacotherapy group, there were more patients who discontinued in with-cost group than overall group (35.9% vs. 33.9%). There were fewer patients who stay on in with-cost than overall group (53.6% vs. 58.3%) and fewer patients who added on another medication (3.7% vs. 4.2%). Among combination pharmacotherapy group, there were more patients who discontinued in with-cost group than overall group (49.3% vs. 47.3%) and more patients who stayed-on (42.7% vs. 40.4%). There were fewer patients who switched to another medication in with-cost than overall group (3.3% vs. 5.5%) and fewer patients who added on to another medication (4.7% vs. 6.9%) (Table A.1).

Table A.1 Comparison Between Treatment Groups Among Overall and With-cost

	Overall (n=7,566)		With Cost (n=2,507)	
	N	%	N	%
Mono-Pharmacotherapy	7145	94.4%	2328	93.9%
Discontinue	2420	33.9%	836	35.9%
Non-Switch	4162	58.3%	1327	53.6%
Switch	260	3.6%	80	3.4%
Add-on	303	4.2%	85	3.7%
Multiple Combination	421	5.6%	150	6.1%
Discontinue	199	47.3%	74	49.3%
Non-Switch	170	40.4%	64	42.7%
Switch	23	5.5%	5	3.3%
Add-on	29	6.9%	7	4.7%

Table A.2 Demographic Characteristics of DPN Patients- With Cost

	Mono-pharmacotherapy (n=2357)		Combination pharmacotherapy (n=150)		P Value
Age(y), mean (standard deviation)	64.4±11.7		60.0±11.7		<0.001
18-44	130	6%	16	11%	<0.001
45-65	1022	43%	82	55%	
>=65	1209	51%	52	35%	
Gender					0.370
Male	1046	44%	72	48%	
Female	1315	56%	78	52%	
Insurance Plan Type					0.096
Commercial	436	18%	37	25%	
Medicaid	560	24%	43	29%	
Medicare	1346	57%	69	46%	
Self- Insured	11	0%	1	1%	
Missing	8	0%	0	0%	
Region					0.111
West	264	11%	13	9%	
Midwest	210	9%	18	12%	
Northeast	759	32%	52	35%	
South	883	37%	61	41%	
Puerto Rico	227	10%	6	4%	
Missing	18	1%	0	0%	
Numbers of Comorbidities					
With1-4 comorbidities	694	29%	39	26%	0.629
With5-7 comorbidities	1170	50%	76	51%	
With >7 comorbidities	497	21%	35	23%	
Pre-index enrollment days (Median)	673	723	0.641		
Post-index enrollment days (Median)	800	791	0.542		

Table A.3 Clinical Co-morbidities of DPN Patients (pre-index: 6 months)- With Cost

	Mono-pharmacotherapy (n=2357)		Combination pharmacotherapy (n=150)		P Value
Cardiovascular disorders	2164	92%	136	91%	0.621
Congestive heart failure	338	14%	23	15%	0.737
Peripheral vascular disease	528	22%	31	21%	0.621
Cerebrovascular disease	305	13%	13	9%	0.127
Coronary heart disease	618	26%	32	21%	0.185
Hypertension	1839	78%	118	79%	0.853
Hyperlipidemia	1615	69%	102	68%	0.894
Diabetes-related condition	595	25%	36	24%	0.734
Retinopathy	277	12%	15	10%	0.517
Nephropathy	404	17%	25	17%	0.881
Mental disorders	398	17%	35	23%	0.043
Depression	324	14%	27	18%	0.145
Bipolar disorder	24	1%	2	1%	0.712
Anxiety	113	5%	12	8%	0.080
Sleep disorders					
Insomnia/sleep disorders	223	9%	14	9%	0.959
Musculoskeletal pain conditions	1479	63%	104	69%	0.105
Arthritis and other arthropathies	753	32%	58	39%	0.088
Rheumatoid arthritis	56	2%	2	1%	0.410
Low back pain	560	24%	48	32%	0.022
Back and neck pain, other than low back pain	274	12%	27	18%	0.020
Rheumatism, excluding the back	915	39%	56	37%	0.717

Table A.4 Clinical Co-morbidities of DPN Patients (post-index: 1 year)- With Cost

	Mono-pharmacotherapy (n=2357)		Combination pharmacotherapy (n=150)		P Value
Cardiovascular disorders	2275	97%	143	95%	0.446
Congestive heart failure	486	21%	29	19%	0.705
Peripheral vascular disease	783	33%	43	29%	0.250
Cerebrovascular disease	455	19%	28	19%	0.848
Coronary heart disease	827	35%	41	27%	0.053
Hypertension	2044	87%	130	87%	0.985
Hyperlipidemia	1866	79%	122	81%	0.526
Diabetes-related condition	839	36%	44	29%	0.119
Retinopathy	433	18%	28	19%	0.928
Nephropathy	581	25%	32	21%	0.359
Mental disorders	553	23%	42	28%	0.205
Depression	463	20%	34	23%	0.368
Bipolar disorder	32	1%	4	3%	0.191
Anxiety	167	7%	11	7%	0.909
Sleep disorders					
Insomnia/sleep disorders	330	14%	31	21%	0.024
Musculoskeletal pain conditions	1780	76%	129	86%	0.003
Arthritis and other arthropathies	1050	45%	92	61%	<0.001
Rheumatoid arthritis	88	4%	0	0%	0.016
Low back pain	778	33%	68	45%	0.002
Back and neck pain, other than low back pain	463	20%	46	31%	0.001
Rheumatism, excluding the back	1219	52%	82	55%	0.483

Table A.5 Characteristics Associated with Combination Pharmacotherapy (demographics)- With Cost

	Odds Ratio	95% CI	P value
Age			
18-44	Ref	Ref	Ref
45-65	0.62	0.34-1.11	0.107
>=65	0.34	0.17-0.67	0.002
Gender			
Male	Ref	Ref	Ref
Female	0.92	0.65-1.28	0.612
Insurance Plan Type			
Commercial	Ref	Ref	Ref
Medicaid	0.86	0.51-1.46	0.588
Medicare	0.89	0.56-1.40	0.612
Self- Insured	1.00	0.12-8.10	0.998
Missing	1	.	.
Region			
West	Ref	Ref	Ref
Midwest	1.72	0.82-3.62	0.154
Northeast	1.33	0.70-2.52	0.391
South	1.47	0.79-2.74	0.227
Puerto Rico	0.67	0.25-1.84	0.441
Missing	1	.	.
Numbers of Comorbidities			
With 1-4 comorbidities	Ref	Ref	Ref
With 5-7 comorbidities	1.27	0.85-1.90	0.240
With >7 comorbidities	1.49	0.92-2.41	0.106

Table A.6 Characteristics Associated with Combination Pharmacotherapy (co-morbidities)- With Cost

	Odds Ratio	95% CI	P value
Cardiovascular disorders	0.87	0.49-1.54	0.623
Diabetes-related condition	0.93	0.63-1.37	0.703
Mental disorders	1.49	1.00-2.21	0.050
Sleep disorders	0.91	0.51-1.61	0.738
Musculoskeletal pain conditions	1.33	0.93-1.91	0.114

Table A.7 Characteristics Associated with Combination Pharmacotherapy (specific co-morbidities)- With Cost

	Odds Ratio	95% CI	P value
Cardiovascular disorders			
Congestive heart failure	1.28	0.77-2.14	0.345
Peripheral vascular disease	0.96	0.63-1.46	0.845
Cerebrovascular disease	0.60	0.33-1.09	0.093
Coronary heart disease	0.73	0.47-1.14	0.168
Hypertension	1.08	0.71-1.65	0.704
Hyperlipidemia	1.01	0.70-1.46	0.954
Diabetes-related condition			
Retinopathy	0.87	0.50-1.51	0.618
Nephropathy	1.01	0.64-1.61	0.960
Mental disorders			
Depression	1.25	0.79-1.98	0.332
Bipolar disorder	1.04	0.24-4.54	0.960
Anxiety	1.58	0.83-3.04	0.166
Sleep disorders			
Insomnia/sleep disorders	0.85	0.47-1.52	0.582
Musculoskeletal pain conditions			
Arthritis and other arthropathies	1.31	0.91-1.89	0.147
Rheumatoid arthritis	0.51	0.12-2.12	0.354
Low back pain	1.35	0.92-1.98	0.121
Back and neck pain, other than low back pain	1.44	0.90-2.30	0.126
Rheumatism, excluding the back	0.83	0.58-1.19	0.312

REFERENCES

1. Association AD. http://www.diabetes.org/diabetes-basics/statistics/. 2014 [cited; Available from:

2. Prevention. CfDCa. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2011.

3. Edwards JL, Vincent AM, Cheng HT, Feldman EL. Diabetic neuropathy: mechanisms to management. Pharmacol Ther. 2008; **120**(1): 1-34.

4. Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005; **28**(4): 956-62.

5. Argoff CE, Cole BE, Fishbain DA, Irving GA. Diabetic peripheral neuropathic pain: clinical and quality-of-life issues. Mayo Clin Proc. 2006; **81**(4 Suppl): S3-11.

6. Baron R, Tolle TR, Gockel U, Brosz M, Freynhagen R. A cross-sectional cohort survey in 2100 patients with painful diabetic neuropathy and postherpetic neuralgia: differences in demographic data and sensory symptoms. Pain. 2009; **146**(1-2): 34-40.

7. Ziegler D. Current concepts in the management of diabetic polyneuropathy. Curr Diabetes Rev. 2011; **7**(3): 208-20.

8. Abbott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care. 2011; **34**(10): 2220-4.

9. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia. 1993; **36**(2): 150-4.

10. Oyibo SO, Pritchard GM, McLay L, James E, Laing I, Gokal R, et al. Blood glucose overestimation in diabetic patients on continuous ambulatory peritoneal dialysis for end-stage renal disease. Diabet Med. 2002; **19**(8): 693-6.

11. Eaton SE, Harris ND, Ibrahim S, Patel KA, Selmi F, Radatz M, et al. Increased sural nerve epineurial blood flow in human subjects with painful diabetic neuropathy. Diabetologia. 2003; **46**(7): 934-9.

12. Quattrini C, Harris ND, Malik RA, Tesfaye S. Impaired skin microvascular reactivity in painful diabetic neuropathy. Diabetes Care. 2007; **30**(3): 655-9.

13. Sorensen L, Molyneaux L, Yue DK. The relationship among pain, sensory loss, and small nerve fibers in diabetes. Diabetes Care. 2006; **29**(4): 883-7.

14. Selvarajah D, Wilkinson ID, Gandhi R, Griffiths PD, Tesfaye S. Microvascular perfusion abnormalities of the Thalamus in painful but not painless diabetic polyneuropathy: a clue to the pathogenesis of pain in type 1 diabetes. Diabetes Care. 2011; **34**(3): 718-20.

15. Gandhi RA, Marques JL, Selvarajah D, Emery CJ, Tesfaye S. Painful diabetic neuropathy is associated with greater autonomic dysfunction than painless diabetic neuropathy. Diabetes Care. 2010; **33**(7): 1585-90.

16. Clearinghouse NDI. Diabetic neuropathies: the nerve damage of diabetes. 2014 [cited 2014 11.12]; Available from: http://diabetes.niddk.nih.gov/dm/pubs/neuropathies/

17. Ritzwoller DP, Ellis JL, Korner EJ, Hartsfield CL, Sadosky A. Comorbidities, healthcare service utilization and costs for patients identified with painful DPN in a managed-care setting. Curr Med Res Opin. 2009; **25**(6): 1319-28.

18. Egede LE, Ellis C. Diabetes and depression: global perspectives. Diabetes Res Clin Pract. 2010; **87**(3): 302-12.

19. Sadosky A, Schaefer C, Mann R, Bergstrom F, Baik R, Parsons B, et al. Burden of illness associated with painful diabetic peripheral neuropathy among adults seeking treatment in the US: results from a retrospective chart review and cross-sectional survey. Diabetes Metab Syndr Obes. 2013; **6**: 79-92.

20. Ziegler D, Schneider E, Boess FG, Berggren L, Birklein F. Impact of comorbidities on pharmacotherapy of painful diabetic neuropathy in clinical practice. J Diabetes Complications. 2014; **28**(5): 698-704.

21. Gore M, Tai KS, Zlateva G, Bala Chandran A, Leslie D. Clinical characteristics, pharmacotherapy, and healthcare resource use among patients with diabetic neuropathy newly prescribed pregabalin or gabapentin. Pain Pract. 2011; **11**(6): 528-39.

22. Gore M, Brandenburg NA, Hoffman DL, Tai KS, Stacey B. Burden of illness in painful diabetic peripheral neuropathy: the patients' perspectives. J Pain. 2006; **7**(12): 892-900.

23. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992; **30**(6): 473-83.

24. Smith BH, Torrance N, Bennett MI, Lee AJ. Health and quality of life associated with chronic pain of predominantly neuropathic origin in the community. Clin J Pain. 2007; **23**(2): 143-9.

25. Hall GC, Morant SV, Carroll D, Gabriel ZL, McQuay HJ. An observational descriptive study of the epidemiology and treatment of neuropathic pain in a UK general population. BMC Fam Pract. 2013; **14**: 28.

26. Dworkin RH, Malone DC, Panarites CJ, Armstrong EP, Pham SV. Impact of postherpetic neuralgia and painful diabetic peripheral neuropathy on health care costs. J Pain. 2010; **11**(4): 360-8.

27. Barrett AM, Lucero MA, Le T, Robinson RL, Dworkin RH, Chappell AS. Epidemiology, public health burden, and treatment of diabetic peripheral neuropathic pain: a review. Pain Med. 2007; **8 Suppl 2**: S50-62.

28. Stewart WF, Ricci JA, Chee E, Hirsch AG, Brandenburg NA. Lost productive time and costs due to diabetes and diabetic neuropathic pain in the US workforce. J Occup Environ Med. 2007; **49**(6): 672-9.

29. Tolle T, Xu X, Sadosky AB. Painful diabetic neuropathy: a cross-sectional survey of health state impairment and treatment patterns. J Diabetes Complications. 2006; **20**(1): 26-33.

30. Stewart WF, Ricci JA, Leotta C, Chee E. Validation of the work and health interview. Pharmacoeconomics. 2004; **22**(17): 1127-40.

31. Albers JW, Herman WH, Pop-Busui R, Feldman EL, Martin CL, Cleary PA, et al. Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Diabetes Care. 2010; **33**(5): 1090-6.

32. Callaghan BC, Hur J, Feldman EL. Diabetic neuropathy: one disease or two? Curr Opin Neurol. 2012; **25**(5): 536-41.

33. Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet. 2010; **376**(9739): 419-30.

34. Callaghan BC, Little AA, Feldman EL, Hughes RA. Enhanced glucose control for preventing and treating diabetic neuropathy. Cochrane Database Syst Rev. 2012; **6**: CD007543.

35. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpaa ML, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc. 2010; **85**(3 Suppl): S3-14.

36. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010; **17**(9): 1113-e88.

37. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. PM R. 2011; **3**(4): 345-52, 52 e1-21.

38. Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings. National Institute for Health and Clinical Excellence. 2010.

39. Tesfaye S, Vileikyte L, Rayman G, Sindrup SH, Perkins BA, Baconja M, et al. Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. Diabetes Metab Res Rev. 2011; **27**(7): 629-38.

40. Ziegler D, Fonseca V. From guideline to patient: a review of recent recommendations for pharmacotherapy of painful diabetic neuropathy. J Diabetes Complications. 2014.

41. Spallone V. Management of painful diabetic neuropathy: guideline guidance or jungle? Curr Diab Rep. 2012; **12**(4): 403-13.

42. Gore M, Sadosky A, Leslie D, Sheehan AH. Selecting an appropriate medication for treating neuropathic pain in patients with diabetes: a study using the U.K. and Germany Mediplus databases. Pain Pract. 2008; **8**(4): 253-62.

43. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007; **132**(3): 237-51.

44. Burke JF, Skolarus LE, Callaghan BC, Kerber KA. Choosing wisely: highest-cost tests in outpatient neurology. Ann Neurol. 2013; **73**(5): 679-83.

45. Argoff CE, Backonja MM, Belgrade MJ, Bennett GJ, Clark MR, Cole BE, et al. Consensus guidelines: treatment planning and options. Diabetic peripheral neuropathic pain. Mayo Clin Proc. 2006; **81**(4 Suppl): S12-25.

46. Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. Basic Clin Pharmacol Toxicol. 2005; **96**(6): 399-409.

47. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med. 1992; **326**(19): 1250-6.

48. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. Am J Med. 2009; **122**(10 Suppl): S22-32.

49. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. Am J Med. 2009; **122**(10): S22-S32.

50. Max MB, Culnane M, Schafer SC, Gracely RH, Walther DJ, Smoller B, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. Neurology. 1987; **37**(4): 589-96.

51. Dunner DL, Wohlreich MM, Mallinckrodt CH, Watkin JG, Fava M. Clinical consequences of initial duloxetine dosing strategies: comparison of 30 and 60 mg QD starting doses. Curr Ther Res Clin Exp. 2005; **66**(6): 522-40.

52. Wernicke J, Lledo A, Raskin J, Kajdasz DK, Wang F. An evaluation of the cardiovascular safety profile of duloxetine: findings from 42 placebo-controlled studies. Drug Saf. 2007; **30**(5): 437-55.

53. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain. 2005; **118**(3): 289-305.

54. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain. 2004; **110**(3): 628-38.

55. Hearn L, Derry S, Phillips T, Moore RA, Wiffen PJ. Imipramine for neuropathic pain in adults. Cochrane Database Syst Rev. 2014; **5**: CD010769.

56. Hearn L, Moore RA, Derry S, Wiffen PJ, Phillips T. Desipramine for neuropathic pain in adults. Cochrane Database Syst Rev. 2014; **9**: CD011003.

57. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev. 2014; **1**: CD007115.

58. McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. Cochrane Database Syst Rev. 2013; **8**: CD006146.

59. Moore RA, Wiffen PJ, Derry S, Toelle T, Rice AS. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2014; **4**: CD007938.

60. O'Connor AB, Noyes K, Holloway RG. A cost-utility comparison of four first-line medications in painful diabetic neuropathy. Pharmacoeconomics. 2008; **26**(12): 1045-64.

61. Davies HT, Crombie IK, Macrae WA. Why use a pain clinic? Management of neurogenic pain before and after referral. J R Soc Med. 1994; **87**(7): 382-5.

62. Torrance N, Ferguson JA, Afolabi E, Bennett MI, Serpell MG, Dunn KM, et al. Neuropathic pain in the community: more under-treated than refractory? Pain. 2013; **154**(5): 690-9.

63. Mendell JR, Sahenk Z. Clinical practice. Painful sensory neuropathy. N Engl J Med. 2003; **348**(13): 1243-55.

64. Daousi C, Benbow SJ, Woodward A, MacFarlane IA. The natural history of chronic painful peripheral neuropathy in a community diabetes population. Diabet Med. 2006; **23**(9): 1021-4.

65. Possidente CJ, Tandan R. A survey of treatment practices in diabetic peripheral neuropathy. Prim Care Diabetes. 2009; **3**(4): 253-7.

66. Gustavsson A, Bjorkman J, Ljungcrantz C, Rhodin A, Rivano-Fischer M, Sjolund KF, et al. Pharmacological treatment patterns in neuropathic pain--lessons from Swedish administrative registries. Pain Med. 2013; **14**(7): 1072-80.

67. Gilron I, Jensen TS, Dickenson AH. Combination pharmacotherapy for management of chronic pain: from bench to bedside. Lancet Neurol. 2013; **12**(11): 1084-95.

68. Mao J, Gold MS, Backonja MM. Combination drug therapy for chronic pain: a call for more clinical studies. J Pain. 2011; **12**(2): 157-66.

69. Kozma CM, Benson C, Slaton TL, Kim MS, Vorsanger GJ. Opioids before and after initiation of pregabalin in patients with diabetic peripheral neuropathy. Curr Med Res Opin. 2012; **28**(9): 1485-96.

70. Gilron I, Max MB. Combination pharmacotherapy for neuropathic pain: current evidence and future directions. Expert Rev Neurother. 2005; **5**(6): 823-30.

71. Mao J. Current challenges in translational pain research. Trends Pharmacol Sci. 2012; **33**(11): 568-73.

72. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. Pain. 2001; **92**(1-2): 147-57.

73. Finnerup NB, Jensen TS. Mechanisms of disease: mechanism-based classification of neuropathic pain-a critical analysis. Nat Clin Pract Neurol. 2006; **2**(2): 107-15.

74. Freeman R, Baron R, Bouhassira D, Cabrera J, Emir B. Sensory profiles of patients with neuropathic pain based on the neuropathic pain symptoms and signs. Pain. 2014; **155**(2): 367-76.

75. Tesfaye S, Wilhelm S, Lledo A, Schacht A, Tolle T, Bouhassira D, et al. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"--a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain. 2013; **154**(12): 2616-25.

76. Bouhassira D, Wilhelm S, Schacht A, Perrot S, Kosek E, Cruccu G, et al. Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: data from the randomized, double-blind, COMBO-DN study. Pain. 2014; **155**(10): 2171-9.

77. IOM (Institute of Medicine). Washington DTNAP. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. 2012/05/04 ed; 2011.

78. Schug SA, Zech D, Dorr U. Cancer pain management according to WHO analgesic guidelines. J Pain Symptom Manage. 1990; **5**(1): 27-32.

79. Lindsay TJ, Rodgers BC, Savath V, Hettinger K. Treating diabetic peripheral neuropathic pain. Am Fam Physician. 2010; **82**(2): 151-8.

80. Raja SN, Haythornthwaite JA. Combination therapy for neuropathic pain--which drugs, which combination, which patients? N Engl J Med. 2005; **352**(13): 1373-5.

81. Hanna M, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. Eur J Pain. 2008; **12**(6): 804-13.

82. Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet. 2009; **374**(9697): 1252-61.

83. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med. 2005; **352**(13): 1324-34.

84. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Database Syst Rev. 2012; **7**: CD008943.

85. Tarride JE CJ, Choiniere M, Rousseau C, Gordon A. The economic burden of neuropathic pain in Canada. Journal of Medical Economics 2006; **9**(1-4): 55-68.

86. Agrawal RP, Goswami J, Jain S, Kochar DK. Management of diabetic neuropathy by sodium valproate and glyceryl trinitrate spray: a prospective double-blind randomized placebo-controlled study. Diabetes Res Clin Pract. 2009; **83**(3): 371-8.

87. Freeman R, Raskin P, Hewitt DJ, Vorsanger GJ, Jordan DM, Xiang J, et al. Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy. Curr Med Res Opin. 2007; **23**(1): 147-61.

88. Gomez-Perez FJ, Choza R, Rios JM, Reza A, Huerta E, Aguilar CA, et al. Nortriptyline-fluphenazine vs. carbamazepine in the symptomatic treatment of diabetic neuropathy. Arch Med Res. 1996; **27**(4): 525-9.

89. Gomez-Perez FJ, Rull JA, Dies H, Rodriquez-Rivera JG, Gonzalez-Barranco J, Lozano-Castaneda O. Nortriptyline and fluphenazine in the symptomatic treatment of diabetic neuropathy. A double-blind cross-over study. Pain. 1985; **23**(4): 395-400.

90. Lynch ME, Clark AJ, Sawynok J. A pilot study examining topical amitriptyline, ketamine, and a combination of both in the treatment of neuropathic pain. Clin J Pain. 2003; **19**(5): 323-8.

91. Lynch ME, Clark AJ, Sawynok J, Sullivan MJ. Topical amitriptyline and ketamine in neuropathic pain syndromes: an open-label study. J Pain. 2005; **6**(10): 644-9.

92. Zin CS, Nissen LM, O'Callaghan JP, Duffull SB, Smith MT, Moore BJ. A randomized, controlled trial of oxycodone versus placebo in patients with postherpetic neuralgia and painful diabetic neuropathy treated with pregabalin. J Pain. 2010; **11**(5): 462-71.

93. Gore M, Zlateva G, Tai KS, Chandran AB, Leslie D. Retrospective evaluation of clinical characteristics, pharmacotherapy and healthcare resource use among patients prescribed pregabalin or duloxetine for diabetic peripheral neuropathy in usual care. Pain Pract. 2011; **11**(2): 167-79.

94. Zhao Y, Wu N, Chen S, Boulanger L, Police RL, Fraser K. Changes in opioid use and healthcare costs among U.S. patients with diabetic peripheral neuropathic pain treated with duloxetine compared with other therapies. Curr Med Res Opin. 2010; **26**(9): 2147-56.

95. Wu N, Chen SY, Hallett LA, Boulanger L, Fraser KA, Patel CK, et al. Opioid utilization and health-care costs among patients with diabetic peripheral neuropathic pain treated with duloxetine vs. other therapies. Pain Pract. 2011; **11**(1): 48-56.

96. Chen S, Wu N, Fraser K, Boulanger L, Zhao Y. Opioid use and healthcare costs among patients with DPNP initiating duloxetine versus other treatments. Curr Med Res Opin. 2010; **26**(10): 2507-16.

97. Chen S, Wu N, Boulanger L, Fraser K, Zhao Z, Zhao Y. Factors associated with pain medication selection among patients diagnosed with diabetic peripheral neuropathic pain: a retrospective study. J Med Econ. 2011; **14**(4): 411-20.

98. Zhao Y, Sun P, Watson P. Medication adherence and healthcare costs among patients with diabetic peripheral neuropathic pain initiating duloxetine versus pregabalin. Curr Med Res Opin. 2011; **27**(4): 785-92.

99. Burke JP, Sanchez RJ, Joshi AV, Cappelleri JC, Kulakodlu M, Halpern R. Health care costs in patients with painful diabetic peripheral neuropathy prescribed pregabalin or duloxetine. Pain Pract. 2012; **12**(3): 209-18.

100. Margolis J, Cao Z, Fowler R, Harnett J, Sanchez RJ, Mardekian J, et al. Evaluation of healthcare resource utilization and costs in employees with pain associated with diabetic peripheral neuropathy treated with pregabalin or duloxetine. J Med Econ. 2010; **13**(4): 738-47.

101. Udall M, Harnett J, Mardekian J. Costs of pregabalin or gabapentin for painful diabetic peripheral neuropathy. J Med Econ. 2012; **15**(2): 361-70.

102. Udall M, Mardekian J, Cabrera J. Identification of patients with painful diabetic peripheral neuropathy who have a favorable cost profile with pregabalin treatment. Pain Pract. 2012; **13**(6): 476-84

103. Johnston SS, Udall M, Cappelleri JC, Johnson BH, Shrady G, Chu BC, et al. Cost comparison of drug-drug and drug-condition interactions in patients with painful diabetic peripheral neuropathy treated with pregabalin versus duloxetine. Am J Health Syst Pharm. 2013; **70**(24): 2207-17.

104. Wu N, Chen S, Boulanger L, Fraser K, Bledsoe SL, Zhao Y. Duloxetine compliance and its association with healthcare costs among patients with diabetic peripheral neuropathic pain. J Med Econ. 2009; **12**(3): 192-202.

105. Pozniak A, Olinger L, Shier V. Physicians' perceptions of reimbursement as a barrier to comprehensive diabetes care. Am Health Drug Benefits. 2010; **3**(1): 31-40.

106. Margolis JM, Johnston SS, Chu BC, Onukwugha E, Hvidsten K, Alvir J, et al. Effects of a Medicaid prior authorization policy for pregabalin. Am J Manag Care. 2009; **15**(10): e95-102.

107. Margolis JM, Cao Z, Onukwugha E, Sanchez RJ, Alvir J, Joshi AV, et al. Healthcare utilization and cost effects of prior authorization for pregabalin in commercial health plans. Am J Manag Care. 2010; **16**(6): 447-56.

108. Suehs BT, Louder A, Udall M, Cappelleri JC, Joshi AV, Patel NC. Impact of a pregabalin step therapy policy among medicare advantage beneficiaries. Pain Pract. 2014; **14**(5): 419-26.

109. Mack A. Examination of the evidence for off-label use of gabapentin. J Manag Care Pharm. 2003; **9**(6): 559-68.

110. Bellows BK, Kuo KL, Biltaji E, Singhal M, Jiao T, Cheng Y, et al. Real-world evidence in pain research: a review of data sources. J Pain Palliat Care Pharmacother. 2014; **28**(3): 294-304.

111. Romanelli RJ, Jukes T, Segal JB. Compliance after switching from branded to generic statins. Pharmacoepidemiol Drug Saf. 2014; **23**(10): 1093-100.

112. Suh HS, Hay JW, Johnson KA, Doctor JN. Comparative effectiveness of statin plus fibrate combination therapy and statin monotherapy in patients with type 2 diabetes: use of propensity-score and instrumental variable methods to adjust for treatment-selection bias. Pharmacoepidemiol Drug Saf. 2012; **21**(5): 470-84.

113. Gore M, Sadosky AB, Leslie DL, Tai KS, Emery P. Therapy switching, augmentation, and discontinuation in patients with osteoarthritis and chronic low back pain. Pain Pract. 2012; **12**(6): 457-68.

114. Statistics. BoL. 2015 [cited 2015 2.5]; Available from: http://www.bls.gov/

115. Bureau UC. Census Bureau Regions and Divisions with State FIPS Codes. 2010 [cited; Available from:

116. Pulkstenis E, Robinson TJ. Two goodness-of-fit tests for logistic regression models with continuous covariates. Stat Med. 2002; **21**(1): 79-93.

117. Lipman AG. Analgesic drugs for neuropathic and sympathetically maintained pain. Clin Geriatr Med. 1996; **12**(3): 501-15.

118. McDonald DC, Carlson K, Izrael D. Geographic variation in opioid prescribing in the U.S. J Pain. 2012; **13**(10): 988-96.

119. Guo JD, Liu GG, Christensen DB, Fu AZ. How well have practices followed guidelines in prescribing antihypertensive drugs: the role of health insurance. Value Health. 2003; **6**(1): 18-28.

120. Manteuffel M, Williams S, Chen W, Verbrugge RR, Pittman DG, Steinkellner A. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. J Womens Health (Larchmt). 2014; **23**(2): 112-9.

121. Bluher M, Kurz I, Dannenmaier S, Dworak M. Pill burden in patients with type 2 diabetes in Germany: subanalysis from the prospective, noninterventional PROVIL study. Clin Diabetes. 2015; **33**(2): 55-61.

122. Luisi AF, Owens NJ, Hume AL. Drugs and the elderly. Philadelphia: Lippincott Williams & Wilkins; 1999.

123. Antunes B, Harding R, Higginson IJ. Implementing patient-reported outcome measures in palliative care clinical practice: a systematic review of facilitators and barriers. Palliat Med. 2014; **28**(2): 158-75.

124. Stone JA, Earl KM, O'Neill BJ, Sharma M, Huynh T, Leblanc K, et al. Aligning health care policy with evidence-based medicine: the case for funding direct oral anticoagulants in atrial fibrillation. Can J Cardiol. 2014; **30**(10): 1245-8.

125. Waddimba AC, Meterko M, Beckman HB, Young GJ, Burgess JF, Jr. Provider attitudes associated with adherence to evidence-based clinical guidelines in a managed care setting. Med Care Res Rev. 2010; **67**(1): 93-116.